PHOSPHODIESTERASE 4 INHIBITORS, INCLUDING N-SUBSTITUTED ANILINE AND DIPHENYLAMINE ANALOGS

This application claims the benefit of U.S. provisional application Serial No. 60/396,725, filed July 19, 2002.

This application is related to application Serial No. 10/051,309 and its provisional applications, Serial No. 60/262,651, filed January 22, 2001, Serial No. 60/267,196, filed February 8, 2001, and Serial No. 60/306,140, filed July 14, 2001, their disclosures being hereby incorporated by reference in their entirety.

Field Of The Invention

The present invention relates generally to the field of phosphodiesterase 4 (PDE4) enzyme inhibition. More specifically this invention relates to selective PDE4 inhibition by novel compounds, e.g., *N*-substituted aniline and diphenylamine analogs, methods of preparing such compounds, compositions containing such compounds, and methods of use thereof.

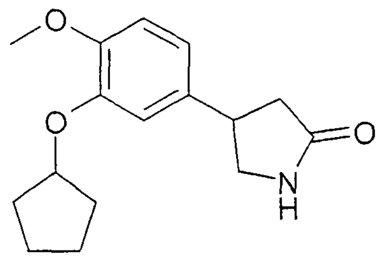
Background Of The Invention

The cyclic nucleotide specific phosphodiesterases (PDEs) represent a family of enzymes that catalyze the hydrolysis of various cyclic nucleoside monophosphates (including cAMP and cGMP). These cyclic nucleotides act as second messengers within cells, and as messengers, carry impulses from cell surface receptors having bound various hormones and neurotransmitters. PDEs act to regulate the level of cyclic nucleotides within cells and maintain cyclic nucleotide homeostasis by degrading such cyclic mononucleotides resulting in termination of their messenger role.

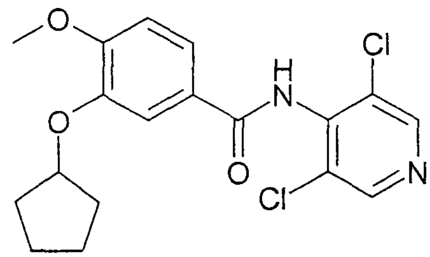
PDE enzymes can be grouped into eleven families according to their specificity toward hydrolysis of cAMP or cGMP, their sensitivity to regulation by calcium, calmodulin or cGMP, and their selective inhibition by various compounds. For example, PDE 1 is stimulated by Ca^{2+}/calmodulin. PDE 2 is cGMP-dependent, and is found in the heart and adrenals. PDE 3 is cGMP-dependent, and inhibition of this enzyme creates positive inotropic activity. PDE is cAMP specific, and its inhibition causes airway relaxation, antiinflammatory and antidepressant activity. PDE 5 appears to be important in regulating cGMP content in vascular smooth muscle, and therefore PDE 5 inhibitors may have cardiovascular activity. Since the PDEs possess distinct biochemical properties, it is likely that they are subject to a variety of different forms of regulation.

PDE4 is distinguished by various kinetic properties including low Michaelis constant for cAMP and sensitivity to certain drugs. The PDE4 enzyme family consists of four genes, which produce 4 isoforms of the PDE4 enzyme designated PDE4A, PDE4B, PDE4C, and PDE4D [See: Wang et al., Expression, Purification, and Characterization of human cAMP-Specific Phosphodiesterase (PDE4) Subtypes A, B, C, and D, *Biochem. Biophys. Res. Comm.*, 234, 320-324 (1997)] In addition, various splice variants of each PDE4 isoform have been identified.

PDE4 isoenzymes are localized in the cytosol of cells and are unassociated with any known membranous structures. PDE4 isoenzymes specifically inactivate cAMP by catalyzing its hydrolysis to adenosine 5'-monophosphate (AMP). Regulation of cAMP activity is important in many biological processes, including inflammation and memory. Inhibitors of PDE4 isoenzymes such as rolipram, piclamilast, CDP-840 and ariflo are powerful antiinflammatory agents and therefore may be useful in treating diseases where inflammation is problematic such as asthma or arthritis. Further, rolipram improves the cognitive performance of rats and mice in learning paradigms.



rolipram



piclamilast

In addition to such compounds as rolipram, xanthine derivatives such as pentoxifylline, denbufylline, and theophylline inhibit PDE4 and have received considerable attention of late for their cognition enhancing effects. cAMP and cGMP are second messengers that mediate cellular responses to many different hormones and neurotransmitters. Thus, therapeutically significant effects may result from PDE inhibition and the resulting increase in intracellular cAMP or cGMP in key cells, such as those located in the nervous system and elsewhere in the body.

Rolipram, previously in development as an anti-depressant, selectively inhibits the PDE4 enzyme and has become a standard agent in the classification of PDE enzyme subtypes. Early work in the PDE4 field focused on depression and inflammation, and has subsequently been extended to include indications such as dementia. [see "The PDE IV Family Of Calcium-Phosphodiesterases Enzymes," John A. Lowe, III, et al., Drugs of the Future 1992, 17(9):799-807 for a general review). Further clinical developments of rolipram and other first-generation PDE4 inhibitors were terminated due to the side effect profile of these compounds. The primary side effect in primates is emesis, while the primary side effects in rodents are testicular degranulation, weakening of vascular smooth muscle, psychotrophic effects, increased gastric acid secretion and stomach erosion.

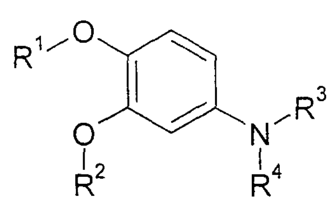
SUMMARY OF THE INVENTION

The present invention relates to novel compounds, e.g., novel *N*-substituted aniline and diphenylamine compounds, that inhibit PDE4 enzymes, and especially have improved side effect profiles, e.g., are relatively non-emetic, (e.g., as compared to the previously discussed prior art compounds). Preferably, the compounds selectively inhibit PDE4 enzymes. The compounds of this invention at the same time facilitate entry into cells, especially cells of the nervous system.

Still further, the present invention provides methods for synthesizing compounds with such activity and selectivity as well as methods of (and corresponding pharmaceutical compositions for) treating a patient, e.g., mammals, including humans, requiring PDE inhibition, especially PDE4 inhibition, for a disease state that involves elevated intracellular PDE 4 levels or decreased cAMP levels, e.g., involving neurological syndromes, especially those states associated with memory impairment, most especially long term memory impairment, as where such memory impairment is due in part to catabolism of intracellular cAMP levels by PDE 4 enzymes, or where such memory impairment may be improved by effectively inhibiting PDE4 enzyme activity.

In a preferred aspect, the compounds of the invention improve such diseases by inhibiting PDE4 enzymes at doses which do not induce emesis.

The present invention includes compounds of Formula I:



wherein

R^1 is H or alkyl having 1 to 4 carbon atoms, which is branched or unbranched and which is unsubstituted or substituted one or more times by halogen (e.g., CH_3, CHF_2, CF_3, etc.); in one preferred embodiment, R^1 is H;

R^2 is alkyl having 1 to 12, preferably 1 to 8 carbon atoms, which is branched or unbranched and which is unsubstituted or substituted one or more times by halogen, hydroxy, cyano, C_{1-4}-alkoxy, oxo or combinations thereof, and wherein optionally one or more $-CH_2CH_2-$ groups is replaced in each case by $-CH=CH-$ or $-C\equiv C-$ (e.g., CH_3, CHF_2, CF_3, methoxyethyl, etc.),

cycloalkyl having 3 to 10, preferably 3 to 8 carbon atoms, which is unsubstituted or substituted one or more times by halogen, hydroxy, oxo, cyano, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, or combinations thereof (e.g., cyclopentyl),

cycloalkylalkyl having 4 to 16, preferably 4 to 12 carbon atoms, which is unsubstituted or substituted in the cycloalkyl portion and/or the alkyl portion one or more times by halogen, oxo, cyano, hydroxy, C_{1-4}-alkyl, C_{1-4}-alkoxy or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

aryl having 6 to 14 carbon atoms, which is unsubstituted or substituted one or more times by halogen, CF_3, OCF_3, alkyl, hydroxy, alkoxy, nitro, methylenedioxy, ethylenedioxy, cyano, or combinations thereof (e.g., methylphenyl, methoxyphenyl, chlorophenyl, etc.),

arylalkyl in which the aryl portion has 6 to 14 carbon atoms and the alkyl portion, which is branched or unbranched, has 1 to 5 carbon atoms, which the arylalkyl radical is unsubstituted or is substituted in the aryl portion one or more times by

halogen, CF_3, OCF_3, alkyl, hydroxy, alkoxy, nitro, cyano, methylenedioxy, ethylenedioxy, or combinations thereof, and wherein in the alkyl portion one or more $-CH_2CH_2-$ groups are each optionally replaced by -CH=CH- or $-C{\equiv}C-$, and one or more $-CH_2-$ groups are each optionally replaced by -O- or -NH- and/or the alkyl portion is optionally substituted by halogen, oxo, hydroxy, cyano, or combinations thereof (e.g., phenylethyl, phenylpropyl, phenylbutyl, methoxyphenylethyl, methoxyphenylpropyl, chlorophenylethyl, chlorophenylpropyl, phenylethenyl, phenoxyethyl, phenoxybutyl, chlorophenoxyethyl, chlorophenylaminoethyl, etc.),

a partially unsaturated carbocyclic group having 5 to 14 carbon atoms, which is unsubstituted or substituted one or more times by halogen, alkyl, alkoxy, hydroxy, nitro, cyano, oxo, or combinations thereof (e.g., cyclohexenyl, cyclohexadienyl, indanyl, tetrahydronaphthenyl, etc.),

a heterocyclic group, which is saturated, partially saturated or unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by halogen, hydroxy, aryl, alkyl, alkoxy, cyano, trifluoromethyl, nitro, oxo, or combinations thereof (e.g., 3-thienyl, 3-tetrahydrofuranyl, 3-pyrrolyl, etc.), or

a heterocycle-alkyl group, wherein the heterocyclic portion is saturated, partially saturated or unsaturated, and has 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, and the alkyl portion is branched or unbranched and has 1 to 5 carbon atoms, the heterocycle-alkyl group is unsubstituted or substituted one or more times in the heterocyclic portion by halogen, OCF_3, hydroxy, aryl, alkyl,

alkoxy, cyano, trifluoromethyl, nitro, oxo, or combinations thereof, wherein in the alkyl portion one or more $-CH_2CH_2-$ groups are each optionally replaced by $-CH=CH-$ or $-C\equiv C-$, and one or more $-CH_2-$ groups are each optionally replaced by -O- or -NH- and/or the alkyl portion is optionally substituted by halogen, oxo, hydroxy, cyano, or combinations thereof (e.g., pyridylethyl, pydridylpropyl, methylpiperazinylethyl, etc.);

R^3 is H,

alkyl having 1 to 8, preferably 1 to 4 carbon atoms, which is branched or unbranched and which is unsubstituted or substituted one or more times with halogen, cyano, C_{1-4}-alkoxy, or combinations thereof (e.g., methyl, ethyl, propyl, etc.),

a partially unsaturated carbocycle-alkyl group wherein the carbocyclic portion has 5 to 14 carbon atoms and the alkyl portion which is branched or unbranched has 1 to 5 carbon atoms, and which is unsubstituted or substituted in the carbocyclic portion one or more times by halogen, alkyl, alkoxy, nitro, cyano, oxo, or combinations thereof, and the alkyl portion is optionally substituted by halogen, C_{1-4}-alkoxy, cyano or combinations thereof (e.g., cyclohexenylmethyl, etc.),

arylalkyl having 7 to 19 carbon atoms, wherein the aryl portion has 6 to 14 carbon atoms and the alkyl portion, which is branched or unbranched, has 1 to 5 carbon atoms, arylalkyl radical is unsubstituted or substituted, in the aryl portion, one or more times by halogen, trifluoromethyl, CF_3O, nitro, amino, alkyl, alkoxy, alkylamino, dialkylamino and/or substituted in the alkyl portion by halogen,

cyano, or methyl (e.g., benzyl, phenethyl, phenpropyl, methylbenzyl, methoxybenzyl, trfluoromethyl, benzyl, methylenedioxobenzyl, etc.), or heteroarylalkyl group, wherein the heteroaryl portion may be partially or fully saturated and has 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, the alkyl portion, which is branched or unbranched, has 1 to 5 carbon atoms, the heteroarylalkyl group is unsubstituted or substituted one or more times in the heteroaryl portion by halogen, alkyl, alkoxy, cyano, trifluoromethyl, CF_3O, nitro, oxo, amino, alkylamino, dialkylamino, or combinations thereof and/or substituted in the alkyl portion by halogen, cyano, or methyl or combinations thereof (e.g., pyridylmethyl, pyridylpropyl, methylpyridylmethyl, chloropyridylmethyl, dichloropyridylmethyl, thienylmethyl, thiazolylmethyl, quinolinylmethyl, isoquinolinylmethyl, piperidinylmethyl, furanylmethyl, imidazolylmethyl, methylimidazolylmethyl, pyrrolylmethyl, etc.);

R^4 is H,

cycloalkyl having 3 to 10, preferably 3 to 8 carbon atoms, which is unsubstituted or substituted one or more times by halogen, hydroxy, oxo, cyano, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, or combinations thereof (e.g., cyclopentyl),

aryl having 6 to 14 carbon atoms and which is unsubstituted or substituted one or more times by halogen, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, alkoxyalkoxy, nitro, methylenedioxy, ethylenedioxy, trifluoromethyl, OCF_3, amino, aminoalkyl, aminoalkoxy, dialkylamino, hydroxyalkyl (eg., hydroxymethyl), hydroxamic acid, pyrrolyl, tetrazole-5-yl, 2(-heterocycle)tetrazole-5-yl (e.g., 2-(2-

tetrahydropyranyl)tetrazole-5-yl), hydroxyalkoxy, carboxy, alkoxycarbonyl (e.g., tert-butyloxycarbonyl, ethoxycarbonyl), cyano, acyl, alkylthio, alkylsulfinyl, alkylsulfonyl, phenoxy, trialkylsilyloxy (eg. *tert*-butyldimethylsilyloxy), R^5-L-, or combinations thereof (e.g., substituted or unsubstituted phenyl, naphthyl, and biphenyl, such as phenyl, methylphenyl, chlorophenyl, fluorophenyl, vinylphenyl, cyanophenyl, methylenedioxophenyl, ethylphenyl, dichlorophenyl, carboxyphenyl, ethoxycarbonylphenyl, dimethylphenyl, hydroxymethylphenyl, nitrophenyl, aminophenyl, etc.), or

heteroaryl having 5 to 10 ring atoms in which at least 1 ring atom is a heteroatom, which is unsubstituted or substituted one or more times by halogen, alkyl, hydroxy, alkoxy, alkoxyalkoxy, nitro, methylenedioxy, ethylenedioxy, trifluoromethyl, amino, aminomethyl, aminoalkyl, aminoalkoxy, dialkylamino, hydroxyalkyl (eg., hydroxymethyl), hydroxamic acid, tetrazole-5-yl, hydroxyalkoxy, carboxy, alkoxycarbonyl (e.g., tert-butyloxycarbonyl, ethoxycarbonyl), cyano, acyl, alkylthio, alkylsulfinyl, alkylsulfonyl, phenoxy, trialkylsilyloxy (eg. *tert*-butyldimethylsilyloxy), R^5-L-, or combinations thereof (e.g., pyridyl, thienyl, pyrazinyl, quinolinyl, isoquinolinyl, pyrimidinyl, imidazolyl, thiazolyl, etc.);

R^5 is H,

alkyl having 1 to 8, preferably 1 to 4 carbon atoms, which is unsubstituted or substituted one or more times with halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, oxo, or combinations thereof (e.g., methyl, ethyl, propyl, etc.),

alkylamino or dialkylamino wherein each alkyl portion has independently 1 to 8, preferably 1 to 4 carbon atoms (e.g., dimethylamino, etc.),

a partially unsaturated carbocycle-alkyl group wherein the carbocyclic portion has 5 to 14 carbon atoms and the alkyl portion has 1 to 5 carbon atoms, which is unsubstituted or substituted, preferably in the carbocyclic portion, one or more times by halogen, alkyl, alkoxy, nitro, cyano, oxo, or combinations thereof (e.g., cyclohexenylmethyl, etc.),

cycloalkyl having 3 to 10, preferably 3 to 8 carbon atoms, which is unsubstituted or substituted one or more times by halogen, hydroxy, oxo, cyano, alkoxy, alkyl having 1 to 4 carbon atoms, or combinations thereof (e.g., cyclopentyl),

cycloalkylalkyl having 4 to 16, preferably 4 to 12 carbon atoms, which is unsubstituted or substituted in the cycloalkyl portion and/or the alkyl portion one or more times by halogen, oxo, cyano, hydroxy, alkyl, alkoxy or combinations thereof (e.g., cyclopentylmethyl, cyclopropylmethyl, etc.),

aryl having 6 to 14 carbon atoms and which is unsubstituted or substituted one or more times by halogen, alkyl, hydroxy, alkoxy, alkoxyalkoxy, nitro, methylenedioxy, ethylenedioxy, trifluoromethyl, amino, aminomethyl, aminoalkyl, aminoalkoxy, dialkylamino, hydroxyalkyl (eg., hydroxymethyl), hydroxamic acid, tetrazole-5-yl, hydroxyalkoxy, carboxy, alkoxycarbonyl (e.g., tert-butyloxycarbonyl, ethoxycarbonyl), cyano, acyl, alkylthio, alkylsulfinyl, alkylsulfonyl, phenoxy, cycloalkyl, aryl, heteroaryl or combinations thereof (e.g., substituted or unsubstituted phenyl and naphthyl, methylphenyl, chlorophenyl, fluorophenyl, vinylphenyl, cyanophenyl, methylenedioxophenyl, ethylphenyl,

dichlorophenyl, carboxyphenyl, ethoxycarbonylphenyl, dimethylphenyl, hydroxymethylphenyl, nitrophenyl, aminophenyl, etc.),

arylalkyl having 7 to 19 carbon atoms, wherein the aryl portion has 6 to 14 carbon atoms and the alkyl portion, which is branched or unbranched, has 1 to 5 carbon atoms, arylalkyl radical is unsubstituted or substituted, in the aryl portion, one or more times by halogen, trifluoromethyl, CF_3O, nitro, amino, alkyl, alkoxy, amino, alkylamino, dialkylamino and/or substituted in the alkyl portion by halogen, cyano, or methyl (e.g., benzyl, phenethyl, phenpropyl, methylbenzyl, methoxybenzyl, trfluoromethyl, benzyl, methylenedioxobenzyl, etc.),

a heterocyclic group, which is saturated, partially saturated or unsaturated, having 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, which is unsubstituted or substituted one or more times by halogen, alkyl, hydroxy, alkoxy, alkoxyalkoxy, nitro, methylenedioxy, ethylenedioxy, trifluoromethyl, amino, aminomethyl, aminoalkyl, aminoalkoxy, dialkylamino, hydroxyalkyl (eg., hydroxymethyl), hydroxamic acid, tetrazole-5-yl, hydroxyalkoxy, carboxy, alkoxycarbonyl (e.g., tert-butyloxycarbonyl, ethoxycarbonyl), cyano, acyl, alkylthio, alkylsulfinyl, alkylsulfonyl, phenoxy, cycloalkyl, aryl, heteroaryl or combinations thereof (e.g., pyridyl, thienyl, pyrazinyl, quinolinyl, isoquinolinyl, pyrimidinyl, imidazolyl, thiazolyl, etc.), or

a heterocycle-alkyl group, wherein the heterocyclic portion is saturated, partially saturated or unsaturated, and has 5 to 10 ring atoms in which at least 1 ring atom is a N, O or S atom, and the alkyl portion which is branched or unbranched and has 1 to 5 carbon atoms, the heterocycle-alkyl group is unsubstituted or

substituted one or more times in the heterocyclic portion by halogen, alkyl, alkoxy, cyano, trifluoromethyl, CF_3O, nitro, oxo, amino, alkylamino, dialkylamino, or combinations thereof and/or substituted in the alkyl portion by halogen, cyano, or methyl or combinations thereof (e.g., pyridylmethyl, pyridylpropyl, methylpridylmethyl, etc.);

L is a single bond or a divalent aliphatic radical having 1 to 8 carbon atoms wherein one or more $-CH_2-$ groups are each optionally replaced by -O-, -S-, -SO-, $-SO_2-$, $-NR^6-$, $-SO_2NH-$, $-NHSO_2-$, $-SO_2NR^6-$, $-NR^6SO_2-$, -CO-, $-NR^6CO-$, $-CONR^6-$, -NHCONH-, -OCONH, -NHCOO-, -SCONH-, -SCSNH-, or -NHCSNH- (e.g., -O-, CH_2-, -CO-, -CO-O-, -O-CO-, -CO-NH-, -NH-CO-, $-CH_2CH_2CH_2-NH-CO-$, $-CH_2-CH_2-O-$, $-SO_2-NH-CH_2CH_2-O-$, $-O-CH_2CH_2-O-$, $-CH_2-NH-CO-$, $-CO-NH-CH_2-$, $-SO_2-NH-$, $-CH_2-NH-SO_2-$, $-CH_2CH_2CH_2-SO_2-NH-$, $-SO_2-$, $-CONHSO_2-$, etc.); and

R^6 is H,

alkyl having 1 to 8, preferably 1 to 4 carbon atoms, which is branched or unbranched and which is unsubstituted or substituted one or more times with halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, oxo, or combinations thereof (e.g., methyl, ethyl, propyl, etc.);

arylalkyl having 7 to 19 carbon atoms, wherein the aryl portion has 6 to 14 carbon atoms and the alkyl portion, which is branched or unbranched, has 1 to 5 carbon atoms, arylalkyl radical is unsubstituted or substituted, in the aryl portion, one or more times by halogen, trifluoromethyl, CF_3O, nitro, amino, alkyl, alkoxy, alkylamino, dialkylamino and/or substituted in the alkyl portion by halogen,

cyano, or methyl (e.g., benzyl, phenethyl, phenpropyl, methylbenzyl, methoxybenzyl, trfluoromethyl, benzyl, methylenedioxobenzyl, etc.);

aryl having 6 to 14 carbon atoms and which is unsubstituted or substituted one or more times by halogen, alkyl, hydroxy, alkoxy, alkoxyalkoxy, nitro, methylenedioxy, ethylenedioxy, trifluoromethyl, amino, aminomethyl, aminoalkyl, aminoalkoxy dialkylamino, hydroxyalkyl (eg., hydroxymethyl), hydroxamic acid, tetrazole-5-yl, hydroxyalkoxy, carboxy, alkoxycarbonyl (e.g., tert-butyloxycarbonyl, ethoxycarbonyl), cyano, acyl, alkylthio, alkylsulfinyl, alkylsulfonyl, (e.g., substituted or unsubstituted phenyl and naphthyl, methylphenyl, chlorophenyl, fluorophenyl, vinylphenyl, cyanophenyl, methylenedioxophenyl, ethylphenyl, dichlorophenyl, carboxyphenyl, ethoxycarbonylphenyl, dimethylphenyl, hydroxymethylphenyl, nitrophenyl, aminophenyl, etc.),

wherein at least one of R^3 and R^4 is other than H; and

pharmaceutically acceptable salts thereof.

In one alternate embodiment, R^1 is H.

In another alternate embodiment, R^4 is cycloalkyl having 3 to 10, preferably 3 to 8 carbon atoms, which is unsubstituted or substituted one or more times by halogen, hydroxy, oxo, cyano, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, or combinations thereof,

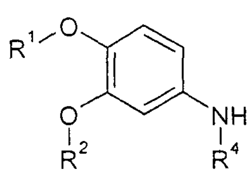
In an alternate embodiment, it is further provided that R^4 is at least monosubstituted by R^5-L- in which L is a single bond or a divalent aliphatic radical having 1 to 8 carbon atoms wherein at least one $-CH_2-$ group is replaced by $-SO_2NR^6-$ or $-NR^6SO_2-$ (e.g., the replacement may result in the divalent radical having no carbon atoms, i.e., where it is a single $-CH_2-$ group which is replaced by $-SO_2NR^6-$ or $-NR^6SO_2-$).

In another embodiment, it is provided that R^4 is at least monosubstituted by R^5-L- in which L is a single bond or a divalent aliphatic radical having 1 to 8 carbon atoms wherein at least one $-CH_2-$ group is replaced by $-NR^6-$, $-SO_2NR^6-$, $-NR^6SO_2-$, $-NR^6CO-$ or $-CONR^6-$ and R^6 is aryl or arylalkyl which are each unsubstituted or substituted (e.g., the replacement may result in the divalent radical having no carbon atoms, as described above).

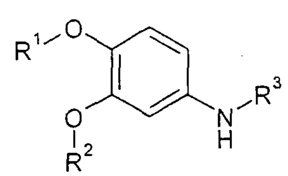
In another embodiment, R^4 is at least monosubstituted by R^5-L in which R^5 is aryl or a heterocyclic group each being substituted by cycloalkyl, aryl or heteroaryl.

In another embodiment, R^4 is at least monosubstituted by R^5-L in which L is a single bond or a divalent aliphatic radical having 1 to 8 carbon atoms wherein at least one $-CH_2-$ group is replaced by -SO- or $-SO_2-$ (e.g., the replacement may result in the divalent radical having no carbon atoms, as described above).

According to a further aspect of the invention there is provided a genus of novel compounds according to the formulas II and III:



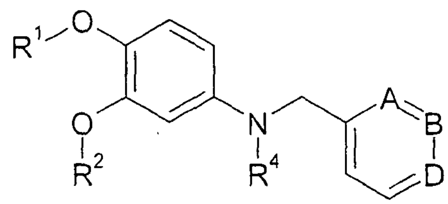
II



III

wherein R^1, R^2, R^3, and R^4 are as defined above. The compounds of this subgenus of formula I not only have PDE4 inhibitory activity, but also are useful as intermediates for preparing compounds of Formula I in which R^3 and R^4 are both other than H.

In addition, preferred compounds of formula I are those of the subformula IV



IV

wherein R^1, R^2, and R^4 are as defined in Formula I and one of A, B and D is N and the others are C. Preferably, B is N. Also, R^4 is preferably pyridyl or phenyl which in each case is substituted or unsubstituted.

In accordance with a further aspect of the invention, the compounds of formula I include the following compounds:

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(5-(2-chloropyridylmethyl))aniline,

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(3-(2-chloropyridylmethyl))aniline,

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(4-(3,5-dimethylisoxazolylmethyl))-aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-aminocarbonylphenyl)-N-(3-pyridylmethyl)aniline,

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(5-(4-chloropyridylmethyl))aniline,

3,4-Bisdifluoromethoxy-N-(3-carboxy-4-chlorophenyl)-N-(3-pyridylmethyl)aniline,

3,4-Bisdifluoromethoxy-N-(4-(1-pyrrol-1-yl)phenyl)-N-(3-pyridylmethyl)aniline,

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(5-(4-methoxypyridylmethyl))aniline,

3-Cyclopentyloxy-4-methoxy-N-phenyl-N-(3-(2-ethoxypyridylmethyl))aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-methylaminocarbonylphenyl)-N-(3-pyridylmethyl)-aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-(2-hydroxyethyl)aminocarbonylphenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(5-(4-chloropyridylmethyl))-aniline,

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline,

3-Cyclopentyloxy-4-methoxy-N-cyclohexylaniline,

3-Cyclopentyloxy-4-hydroxy-N-(3-*tert*-butyloxycarbonylphenyl)-N-(3-pyridylmethyl))-aniline,

3-Cyclopentyloxy-4-hydroxy-N-(3-carboxyphenyl)-N-(3-pyridylmethyl))aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-*tert*-butyloxycarbonylphenyl)-N-(3-pyridylmethyl))-aniline,

4-Methoxy-3-(*R*)-tetrahydrofuryloxy-N-(3-carboxy-4-chlorophenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxyphenyl)-N-(4-(3-chloropyridylmethyl))-aniline,

3-Cyclopentyloxy-4-methoxy-N-phenyl-N-(4-(3-chloropyridylmethyl)aniline,

4-Methoxy-3-(*R*)-tetrahydrofuryloxy-N-(3-carboxyphenyl)-N-(4-pyridylmethyl)aniline,

4-Methoxy-3-(*R*)-tetrahydrofuryloxy-N-(3-pyridyl)-N-(4-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(4-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxy-3-chlorophenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxy-3-methylphenyl)-N-(3-pyridylmethyl)-aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxy-3-fluorophenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-chlorophenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-fluorophenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))-aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))-aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(4-(3-chloropyridylmethyl))-aniline,

4-Methoxy-3-(*R*)-tetrahydrofuryloxy-N-(4-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline,

4-Methoxy-3-(*R*)-tetrahydrofuryloxy-N-(3-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-methylphenyl)-N-(3-pyridylmethyl)-aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-amino-3-carboxyphenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-trifluoromethylphenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-acetamido-3-carboxyphenyl)-N-(3-pyridylmethyl)aniline,

3-Cyclopentyloxy-4-methoxy-N-(4-(N,N-bis(2,4-dimethoxy)benzyl)-aminosulfonylphenyl)-N-(3-pyridylmethyl)aniline,

Methyl N-(3-cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-bromoaniline ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N-piperidinylmethyl)aniline ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N-morpholinomethyl)aniline ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N,N-diethylamino)methyl)aniline ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-methylthioaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylthioaniline ,

N-(3-(2-Hydroxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-2-aminoisonicotinic acid ,

N-(3-Hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-[3-(3-Hydroxy)cyclopentyloxy-4-methoxyphenyl]-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-amino-2-chlorobenzoic acid,

N-(3,4-Bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-amino-6-methylbenzoic acid ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-4-aminobenzoic acid ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-(1,3-dimethylpyrazolylmethyl)-3-aminobenzoic acid,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-5-triflluoromethyl-3-aminobenzoic acid ,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-6-triflluoromethyl-3-aminobenzoic acid ,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-4-aminobenzoic acid,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-Cyclobutyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-Cyclohexyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-Cycloheptyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(4-Methoxy-3-(4-pyranyloxy)phenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-[2.2.2-Bicyclooctanyl]oxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid ,

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(2,6-difluorobenzyl)-3-aminobenzoic acid ,

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(4-(3,5-dimethylisoxazolyl))-3-aminobenzoic acid ,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoic acid ,

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoic acid ,

N-(3,4-Bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoic acid ,

N-(3-Cyclobutyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid,

N-(3-Cyclohexyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(4-Methoxy-3-(2-(2-Pyridylethoxy))phenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(3,4-Dimethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(3-Isopropoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid ,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(2-(3-pyridylethyl))-3-aminobenzoic acid,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-chloro-4-(5-(2H)-tetrazolyl)aniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-chloro-4-(5-(2H)-tetrazolyl)aniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridyl)methyl)-4-(5-(2H)-tetrazolyl)aniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)aniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-N-methyl-1-piperazinyl)aniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1-piperazinyl)aniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N,N-diethylamino)aniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methanesulfonylaniline,

N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-methylsulfonylaniline,

N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-chloro-3-pyridylmethyl)-3-aminobenzoic acid,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-fluorobenzyl)-4-aminobenzoic acid,

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid,

N-(3,4-Dimethoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-[4-Methoxy-3-(1-propyl)oxyphenyl]-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-[4-Methoxy-3-(2-propyl)oxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-(3-Cyclopropylethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-(3-Cyclobutylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-hydroxymethylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-hydroxymethylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-piperidinyl)sulfonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-methylsulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-(2-methylphenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-phenylsulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-phenylsulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridylmethyl)-4-phenylsulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridylmethyl)-4-methylsulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-ethylsulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-methoxyphenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-phenylsulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-phenylsulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-3-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-methylsulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-phenylsulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,4-difluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3,4-difluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1,1-dimethylethyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(5-chloro-2-thienyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-thienyl)sulfonylaminocarbonylaniline,

N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-cyanophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2-thienyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-cyanophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(2,6-difluorobenzyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,4-difluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3,4-difluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-fluorobenzyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline,

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-ethylsulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(3-cyanophenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(2,4-difluorophenyl)sulfonylaminocarbonylaniline,

N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline,

N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-ethylsulfonylaminocarbonylaniline,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3,4-difluorophenyl)sulfonylaminocarbonylaniline,

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(2-thienyl)sulfonylaminocarbonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-cyclopentylmethylcarbonylaminosulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)carbonylaminosulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1-ethyl-5-methylpyrazol-4-yl)carbonylaminosulfonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-(4-methylpiperazin-1-yl)sulfonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-(4-morpholinyl)sulfonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-methylpiperazin-1-yl)sulfonylaniline,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-(4-methylpiperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-methylpiperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-(4-morpholinyl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-ethylpiperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-cyclohexylpiperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3,5-dimethylpiperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-(2-pyridyl)piperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-(4-fluorophenyl)piperazin-1-yl)sulfonylaniline,

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,5-dimethylpyrrol-1-yl)sulfonylaniline,

pharmaceutically acceptable salts thereof,

wherein compounds that are optically active can be in the form of their separate enantiomers or mixtures thereof, including racemic mixtures.

The compounds of the present invention are effective in inhibiting, or modulating the activity of PDE4 in animals, e.g., mammals, especially humans. These compounds exhibit neurological activity, especially where such activity affects cognition, including long term memory. These compounds will also be effective in treating diseases where decreased cAMP levels are involved. This includes but is not limited to inflammatory diseases. These compounds may also function as antidepressants, or be useful in treating cognitive and negative symptoms of schizophrenia.

Assays for determining PDE inhibiting activity as well as selectivity of PDE 4 inhibiting activity and selectivity of inhibiting PDE 4 isoenzymes are known within the art. See, e.g., U.S. Patent No. 6,136,821, the disclosure of which is incorporated herein by reference.

According to a further aspect of the invention there are provided compounds useful as intermediates for the production of the PDE4 inhibitors described herein (e.g., PDE4 inhibitors of Formula I) and/or useful for the synthesis of radio-labeled analogs of the PDE4 inhibitors with in this application.

Thus, there are provided intermediate compounds which correspond to compounds of Formula I, wherein R^2, R^3, and R^4 are as previously defined for Formula I, but R^1 is H, *tert*-butyldimethylsilyl-, or a suitable phenolic protecting group. Suitable phenolic protecting groups are described, for example, in Greene, T.W. and Wuts, P.G.M., Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1999, pp. 246-293. These intermediates are also

useful for the synthesis of radio-labeled compounds, such as where R^1 is ^3H_3C-, $^{14}CH_3$- or $^{11}CH_3$-, for example by removing the protecting group and reacting the resultant compound in which R^1 is H with suitable radio-labelled reagents. Such radio-labeled compounds are useful for determining compound tissue distribution in animals, in PET imaging studies, and for in vivo, ex vivo, and in vitro binding studies.

Also provided are intermediate compounds which correspond to compounds of Formula I, wherein R^1, R^3, and R^4 are as previously defined for Formula I, but R^2 is H, *tert*-butyldimethylsilyloxy-, or a suitable phenolic protecting group. Suitable phenolic protecting groups are described, for example, in Greene, T.W. and Wuts, P.G.M., Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1999, pp. 246-293. Compounds in which R^2 is H are useful as intermediates, for example, as scaffolds for parallel or combinatorial chemistry applications. Further, these compounds are useful for the introduction of radio-labels such as ^3H, ^{14}C, or ^{11}C.

As previously described, compounds according to formula II, wherein R^1, R^2 and R^4 are as previously described are useful intermediates for the production of compounds according to formula I where in R^3 is other than H.

Also, as previously described, compounds according to formula III, wherein R^1, R^2 and R^3 are as previously described are useful intermediates for the production of compounds according to formula I where in R^4 is other than H.

Halogen herein refers to F, Cl, Br, and I. Preferred halogens are F and Cl.

Alkyl, as a group or substituent per se or as part of a group or substituent (e.g., alkylamino, trialkylsilyloxy, aminoalkyl, hydroxyalkyl), means a straight-chain or branched-chain aliphatic hydrocarbon radical having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms,

especially 1 to 4 carbon atoms. Suitable alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, and dodecyl. Other examples of suitable alkyl groups include 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, ethylmethylpropyl, trimethylpropyl, methylhexyl, dimethylpentyl, ethylpentyl, ethylmethylbutyl, dimethylbutyl, and the like.

Substituted alkyl groups are alkyl groups as described above which are substituted in one or more positions by halogens, oxo, hydroxyl, C1-4-alkoxy and/or cyano. Halogens are preferred substituents, especially F and Cl.

Alkoxy means alkyl-O- groups and alkoxyalkoxy means alkyl-O-alkyl-O- groups in which the alkyl portions are in accordance with the previous discussion. Suitable alkoxy and alkoxyalkoxy groups include methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy methoxymethoxy ethoxymethoxy, propoxymethoxy, and methoxyethoxy. Preferred alkoxy groups are methoxy and ethoxy. Similarly, alkoxycarbonyl means alkyl -O-CO- in which the alkyl portion is in accordance with the previous discussion. Examples include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and tert-butoxycarbonyl.

Cycloalkyl means a monocyclic, bicyclic or tricyclic nonaromatic saturated hydrocarbon radical having 3 to 10 carbon atoms, preferably 3 to 8 carbon atoms, especially 3 to 6 carbon atoms. Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, 1-decalin, adamant-1-yl, and adamant-2-yl. Other suitable cycloalkyl groups include spiropentyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, spiro[2.4]heptyl, spiro[2.5]octyl, bicyclo[5.1.0]octyl, spiro[2.6]nonyl, bicyclo[2.2.0]hexyl, spiro[3.3]heptyl, bicyclo[4.2.0]octyl, and spiro[3.5]nonyl. Preferred cycloalklyl groups are

cyclopropyl, cyclopentyl and cyclohexyl. The cycloalkyl group can be substituted, for example, substituted by halogens and/or alkyl groups.

Cycloalkylalkyl refers to cycloalkyl-alkyl radicals in which the cycloalkyl and alkyl portions are in accordance with previous discussions. Suitable examples include cyclopropylmethyl and cyclopentylmethyl.

Aryl, as a group or substituent per se or as part of a group or substituent, refers to an aromatic carbocyclic radical containing 6 to 14 carbon atoms, preferably 6 to 12 carbon atoms, especially 6 to 10 carbon atoms. Suitable aryl groups include phenyl, naphthyl and biphenyl. Substituted aryl groups include the above-described aryl groups which are substituted one or more times by, for example, halogen, alkyl, hydroxy, alkoxy, nitro, methylenedioxy, ethylenedioxy, amino, alkylamino, dialkylamino, hydroxyalkyl, hydroxyalkoxy, carboxy, cyano, acyl, alkoxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, and phenoxy.

Arylalkyl refers to an aryl-alkyl-radical in which the aryl and alkyl portions are in accordance with the previous descriptions. Suitable examples include benzyl, 1-phenethyl, 2-phenethyl, phenpropyl, phenbutyl, phenpentyl, and napthylmethyl.

Heteroaryl refers to an aromatic heterocyclic group having one or two rings and a total number of 5 to 10 ring atoms wherein at least one of the ring atoms is a heteroatom. Preferably, the heteroaryl group contains 1 to 3, especially 1 or 2, hetero-ring atoms which are selected from N, O and S. Suitable heteroaryl groups include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, dithialyl, oxathialyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, benzofuranyl, isobenzofuranyl, thionaphthenyl, isothionaphthenyl, indolyl, isoindolyl, indazolyl,

benzisoxazolyl, benzoxazolyl, benzthiazolyl, benzisothiazolyl, purinyl, benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, naphthyridinyl, and benzoxazinyl, e.g., 2-thienyl, 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, and 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl.

Substituted heteroaryl refers to the heteroaryl groups described above which are substituted in one or more places by, for example, halogen, aryl, alkyl, alkoxy, carboxy, methylene, cyano, trifluoromethyl, nitro, oxo, amino, alkylamino, and dialkylamino.

Heterocycles include heteroaryl groups as described above as well as non-aromatic cyclic groups containing at least one hetero-ring atom, preferably selected from N, S and O, for example, tetrahydrofuranyl, piperidinyl, and pyrrolidinyl.

Heterocycle-alkyl refers to a heterocycle-alkyl-group wherein the heterocyclic and alkyl portions are in accordance with the previous discussions. Suitable examples are pyridylmethyl, thienylmethyl, pyrimidinylmethyl, pyrazinylmethyl, and isoquinolinylmethyl.

Partially unsaturated carbocyclic structures are non-aromatic monocyclic or bicyclic structures containing 5 to 14 carbon atoms, preferably 6 to 10 carbon atoms, wherein the ring structure(s) contains at least one C=C bond. Suitable examples are cyclopentenyl, cyclohexenyl, cyclohexadienyl, tetrahydronaphthenyl and indan-2-yl.

Alkenyl refers to straight-chain or branched-chain aliphatic radicals containing 2 to 12 carbon atoms in which one or more -CH_2-CH_2- structures are each replaced by -CH=CH-. Suitable alkenyl groups are ethenyl, 1-propenyl, 2-methylethenyl, 1-butene, 2-butene, 1-pentenyl, and 2-pentenyl.

Alkynyl refers to straight-chain or branched-chain aliphatic radicals containing 2 to 12 carbon atoms in which one or more $-CH_2-CH_2-$ structures are each replaced by $-C\equiv C-$. Suitable alkynyl groups are ethynyl, propynyl, 1-butynyl, and 2-butynyl.

Acyl refers to alkanoyl radicals having 1 to 13 carbon atoms in which the alkyl portion can be substituted by halogen, alkyl, aryl and/or alkoxy, or aroyl radicals having 7 to 15 carbon atoms in which the aryl portion can be substituted by, for example, halogen, alkyl and/or alkoxy. Suitable acyl groups include formyl, acetyl, propionyl, butanoyl and benzoyl.

Substituted radicals preferably have 1 to 3 substituents, especially 1 to 2 substituents.

In the compounds of Formula I, R^1 preferably is an alkyl group having preferably 1 to 4 carbon atoms which is optionally substituted by halogen, preferably fluorine or chlorine. In particular, R^1 is preferably methyl or difluoromethyl.

R^2 is preferably cycloalkyl, particularly cyclopentyl.

R^2 is also preferably aryl or arylalkyl, particularly substituted or unsubstituted phenyl or phenylalkyl, such as phenyl, methylphenyl, methoxyphenyl, chlorophenyl, phenethyl, phenpropyl, phenbutyl, phenylethenyl, phenoxyethyl, phenoxypropyl, phenoxybutyl, chlorophenylethyl, methoxyphenyl ethyl, chlorophenylethenyl, chlorophenoxyethyl, chlorophenypropyl, methoxyphenpropyl, methoxyphenbutyl, chlorophenbutyl, nitrophenbutyl, chlorophenylaminoethyl, and the like.

R^2 is also preferably a partially unsaturated carbocyclic groups, which is unsubstituted or substituted, particularly cyclohexenyl, cyclohexadienyl, indan-2-yl.

R^2 is also preferably an alkyl group having 1 to 8 carbon atoms, especially 1 to 4 carbon atoms, which is substituted or unsubstituted, e.g., methyl, difluoromethyl, trifluoromethyl, and methoxyethyl.

R^2 is also preferably a heterocyclic or heterocycle-alkyl group, particularly radicals in which the heterocyclic group has 5 to 6 ring atoms and 1 to 2 hetero-ring atoms selected from N, O and S, e.g., tetrahydrofuranyl, pyrrolidinyl, pyrrolyl, pyridylmethyl, pyridylethyl, pyridylpropyl, piperazinylmethyl, piperazinylethyl, methylpiperazinylethyl and the like.

Preferred R^2 include cyclopentyl, tetrahydrofuranyl, CHF_2, methoxyethyl, cyclopropylmethyl, phenethyl, phenpropyl, phenylethenyl, phenoxyethyl, phenoxybutyl, phenylaminoethyl, indan-2-yl, pyridylethyl, and pyridylpropyl.

R^3 is preferably hydrogen, alkyl having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, or n-butyl), arylalkyl (e.g., substituted or unsubstitituted benzyl, phenethyl, and phenpropyl), or a heteroarylalkyl group (e.g., substituted or unsubstituted pyridylmethyl, furanylmethyl, thienylmethyl, pyrrolylmethyl, oxazolylmethyl, isoxazolylmethyl, pyrimidinylmethyl, thiazolylmethyl, isoquinolinylmethyl and quinolinylmethyl). Preferred substituents for aryl and heteroaryl portions of R^3 are F, Cl, CH_3, C_2H_5, OCH_3, and CN.

R^4 is preferably aryl, or heteroaryl, especially phenyl, naphthyl, biphenyl, furanyl, pyrazinyl, pyrimidinyl, pyridyl, quinolinyl, and isoquinolinyl, which in each case is unsubstituted or is substituted one or more times. Preferred substituents are OH, F, Cl, CF_3, alkyl (such as methyl or ethyl), alkoxy (such as methoxy and ethoxy), NH_2, $NHCOCH_3$, CN, vinyl, CH_2OH, CONHOH, $CONHCH_2CH_2OH$, $CONH_2$, $CONHCH_3$, methylenedioxy, COOH, COOalkyl, pyrrolyl, and combinations thereof.

R^4 can also preferably be cycloalkyl, e.g., cyclohexyl.

In addition, when R^4 is aryl, especially, phenyl, preferred substituents include R^5-L-, e.g., R^5-, R^5-O-, R^5-CO-, R^5-NH-CO-, R^5-SO_2-NH-, R^5-SO_2-NR^6-, R^5-NHR^6-SO_2-, R^5-SO_2-NH-

alkylene-O-, NH_2-alkyl-NH-CO-, R^5-alkylene-NH-CO-, alkyl-CO-NH-alkyl, as well as methyl, ethyl, Cl, F, CN, OCH_3, CF_3, amino, nitro, $HOCH_2$ and COOH.

In R^5-SO_2-NR^6-, R^5-NHR^6-SO_2-, R^6 is preferably aryl or arylalkyl, e.g., substituted or unsubstituted phenyl or benzyl.

When R^4 is aryl substituted by R^5-SO_2-NH- it is preferably a substituted phenyl group and R^5 is preferably methyl, ethyl, propyl or phenyl.

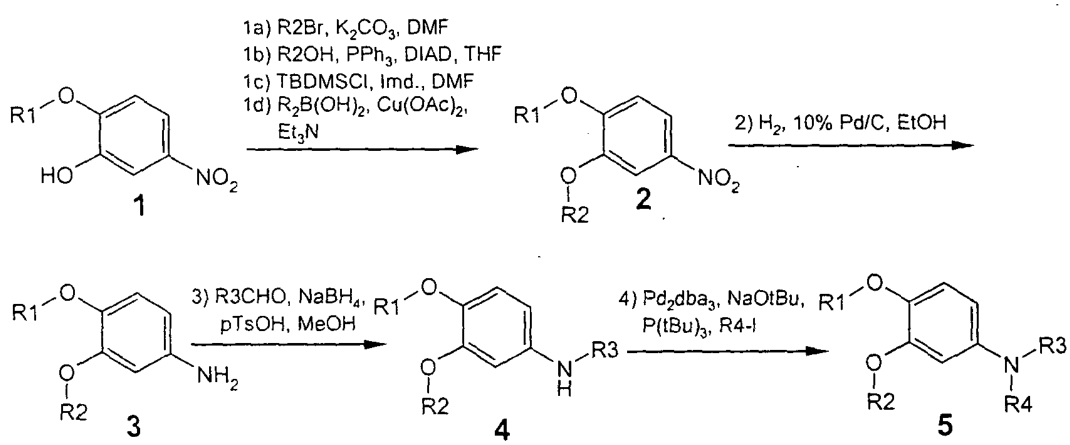
When R^4 is aryl substituted by R^5-SO_2-NH-alkylene-O- it is preferably a substituted phenyl. In such cases, R^5 is preferably methyl, ethyl, propyl or phenyl and alkylene is preferably -CH_2-, -CH_2CH_2- or -$CH_2CH_2CH_2$-.

When R^4 is aryl substituted by R^5-L- it is preferably substituted phenyl. In such cases, preferred R^5 groups include benzyl, tetrazolyl, oxazinyl, piperazinyl, methylpiperazinyl, pyridyl, methylpyridyl, pyrrolinyl, methylpyrrolinyl, piperadinyl, or methylpiperadinyl, and L is preferably a single bond, -O-, -CO-, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2-O-, -CH_2CH_2-O-, -$CH_2CH_2CH_2$-O-, -CH_2-NH-CH_2CH_2-O-, -CO-NH-, -NH-CO-, -SO_2-NR^6-, -NHR^6-SO_2-, -SO_2-, or -$CONHSO_2$-.

Preferred aspects include pharmaceutical compositions comprising a compound of this invention and a pharmaceutically acceptable carrier and, optionally, another active agent as discussed below; a method of inhibiting a PDE4 enzyme, especially an isoenzyme, e.g., as determined by a conventional assay or one described herein, either in vitro or in vivo (in an animal, e.g., in an animal model, or in a mammal or in a human); a method of treating neurological syndrome, e.g., loss of memory, especially long-term memory, cognitive impairment or decline, memory impairment, etc. a method of treating a disease state modulated by PDE4 activity, in a mammal, e.g., a human, e.g., those mentioned herein.

The compounds of the present invention may be prepared conventionally. Some of the processes which can be used are described below. All starting materials are known or can be conventionally prepared from known starting materials.

SCHEME 1



Starting nitrophenols of the type 1 are either commercially available (e.g., R1 = CH3) or prepared by published procedures (e.g., R1 = CHF2 or both R1 and R2 = CHF2, see Mueller, Klaus-Helmut. Eur. Pat. Appl. (1994), 8 pp. CODEN: EPXXDW EP 626361A1; Touma, Toshihiko; Asai, Tomoyuki. Jpn. Kokai Tokyo Koho (1999), 6 pp. CODEN: JKXXAF JP 11071319 A2; Platonov, Andrew; Seavakov, Andrew; Maiyorova, Helen; Chistokletov, Victor. Int. Symp. Wood. Pulping Chem., 1995, 8th, 3, 295-299; Christensen, Siegfried Benjamin; Dabbs, Steven; Karpinski, Joseph M. PCT Int. Appl. (1996), 12 pp. CODEN: PIXXD2 WO 9623754 A1 19960808). Aniline intermediates 3 are produced in two steps; first, an addition reaction provides intermediate 2, followed by reduction of the nitro group. Intermediate nitro compounds 2 can be prepared by numerous published procedures, such as by Mitsunobu reactions or standard alkylation reactions. Compounds where R2 is aryl or heteroaryl can be prepared by copper catalyzed reactions with aryl or heteroaryl iodides under Ullman conditions or by coupling aryl-, vinyl-, or heteroaryl- boronic acids with phenol 2 in the presence of a

copper catalyst (e.g., $Cu(OAc)2$) and base such as TEA. Mitsunobu reaction between an appropriately substituted nitrophenol and a primary or secondary alcohol using an azodicarboxylate (e.g., DEAD, DIAD), and a suitable phosphine (e.g., Ph3P, Bu3P) provides alkylated nitrophenols 2. Mitsunobu reactions are general performed in aprotic solvents such as dichloromethane or THF. Alternatively, alkylation can be achieved by the reaction between an appropriately substituted nitrophenol and an alkyl halide in the presence of a base (e.g., K2CO3 or NaH) in a polar aprotic solvent (e.g., DMF or CH3CN).

Nitrocatechols 2 are subsequently reduced to the corresponding anilines 3 by methods standard in the art such as by hydrogenation using a suitable catalyst (e.g., Pd on carbon) in a polar protic solvent (e.g., MeOH or EtOH) under an atmosphere of hydrogen. Alternatively, nitrocatechols 3 can be reduced by using a hydride source (e.g., NaBH4) and a transition metal catalyst (e.g., NiCl2, Pd on carbon) or by using metals (e.g., Zn, Sn, Fe) in mineral acid solutions (e.g., HCl) to produce the corresponding anilines. Generally polar protic solvents such as ethanol or methanol are used in these reactions.

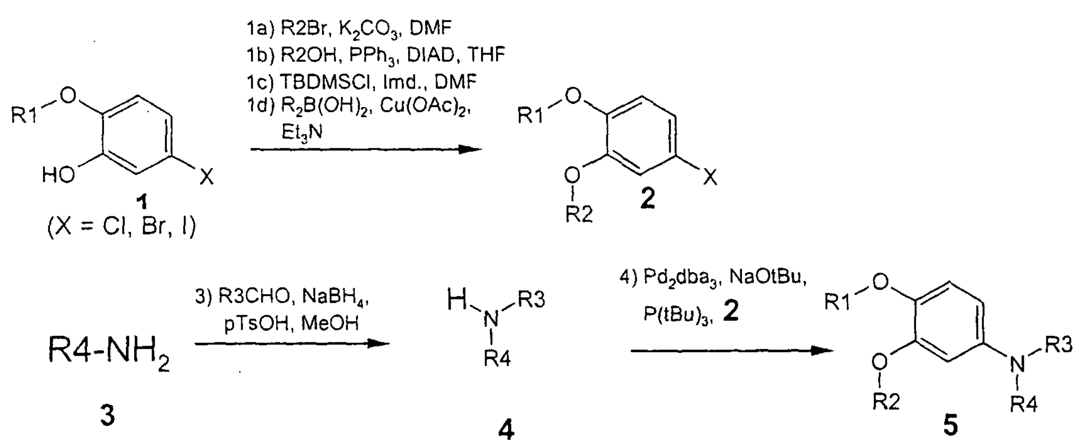
N-Arylalkylanilines 4 are synthesized by standard methods in the art such as by reductive amination reaction, alkylation reaction, or by reduction of corresponding amides. For example, the reductive amination reaction of an aryl or arylalkyl aldehyde with appropriately substituted anilines in the presence of a borohydride reducing agent such as NaBH4 or NaBH3CN with an acid catalyst such as acetic acid or pTsOH provides desired N-arylalkylanilines. These reactions generally take place in polar protic solvents such as methanol, ethanol, isopropanol, n-propanol and the like.

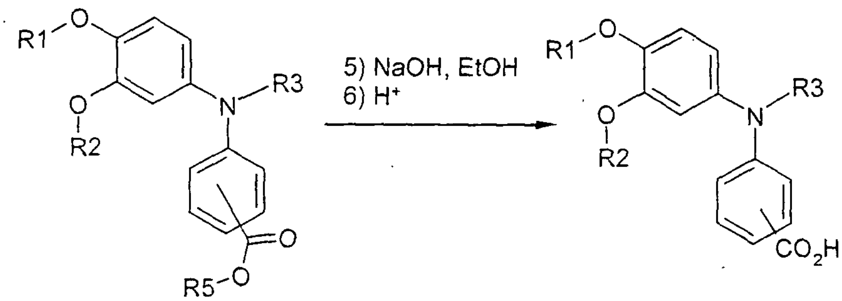
N-Arylalkylanilines 4 readily undergo N-arylation by methods standard to the art including Ullman coupling reaction, metal-catalyzed coupling, or aromatic nucleophilic

substitution reaction. For example, the metal catalyzed reaction between an N-benzylaniline and an aryl halide using a palladium catalyst, (e.g., Pd2dba3), a bulky electron rich phosphine ligand (e.g., tributylphosphine), and suitable base (e.g., NaOtBu) provides N-Arylalkyldiphenylamines. Nickel and copper catalysts have been employed as well. Solvents useful in this reaction include non-polar aprotic solvents such as toluene, benzene, xylenes, tetrahydrofuran, and ether. When synthesizing compounds of the type 5 wherein R4 is an alkoxycarbonylphenyl, it is advantageous that amine 4 is coupled with 1.1 equivalents of tert-butyl 3-iodobenzene and that 22 mol % of (tBu)3P, 5.5 mol % of Pd2(dba)3 and 1.3 equivalents of tBuONa are used.

Alternatively, targets of general formulae I, represented as structure 5 in the following scheme can be prepared by N-arylation reaction between catechol ether halides of general structure 2 and N-substituted anilines of general structure 4 under conditions standard to the art (see previous scheme). Intermediates 2 and 4 can be synthesized by numerous methods standard in the art, or as represented in the scheme.

SCHEME 2

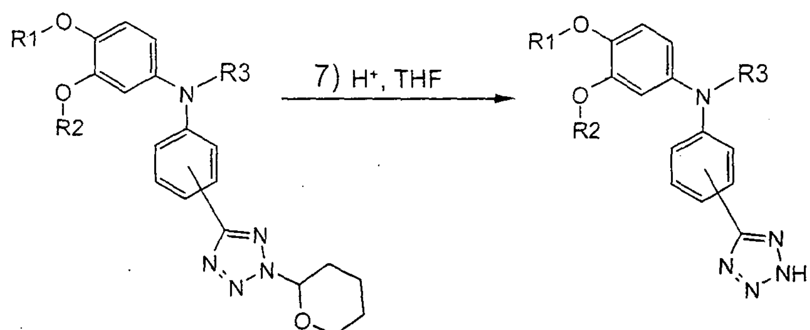




6 **7**

Carboxylic ester intermediates **6** can be hydrolyzed under acidic or basic conditions to give the corresponding carboxylic acids **7**. For example, an ethyl ester (R5 = Et) can be hydrolyzed using a mixture of aqueous base (e.g., NaOH, KOH) and a water miscible solvent (e.g., EtOH, THF). While *t*-Butyl esters (R5 = *t*-butyl) can be hydrolyzed using an aqueous acid (e.g., HCl, formic acid, TFA) in a water miscible organic solvent, if necessary.

SCHEME 3



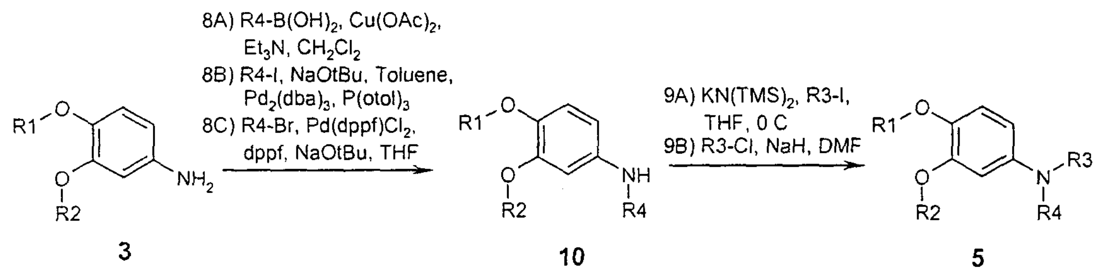
8 **9**

Coupling of protected tetrazole bromo or iodobenzenes (e.g., 5-(3-iodophenyl)-2-(2-tetrahydropyran)tetrazole) with *N*-substituted aniline derivatives **4** produce THP-protected tetrazoles **8**. Hydrolysis of THP-protected tetrazoles **8** can be accomplished by using an aqueous acid, such as HCl in water and a miscible solvent such as THF or EtOH to provide tetrazoles **9**. Further, THP tetrazoles **8** can also be oxidatively cleaved using reagents such as CAN and DDQ

in halognenated hydrocarbon solvents such as dichloromethane, chloroform, dichloroethane and the like to yield tetrazoles **9**.

Alternatively, tetrazole analogs 9 can be prepared from the corresponding nitriles by treatment with azide ion (e.g., KN3, NaN3, etc.) and a proton source (e.g., NH4Cl) in a polar aprotic solvent such as DMF. They also may be prepared by treatment with an azide ion and a Lewis acid (e.g., ZnBr2) in water, using a water miscible co-solvent such as isopropanol if necessary. Another method of preparation is by treatment of a nitrile with tin or silicon azides (e.g., Me3SiN3, Bu3SnN3) in an aprotic organic solvent such as benzene, toluene, dichloromethane, dichloroethane, ether, THF, and the like.

SCHEME 4

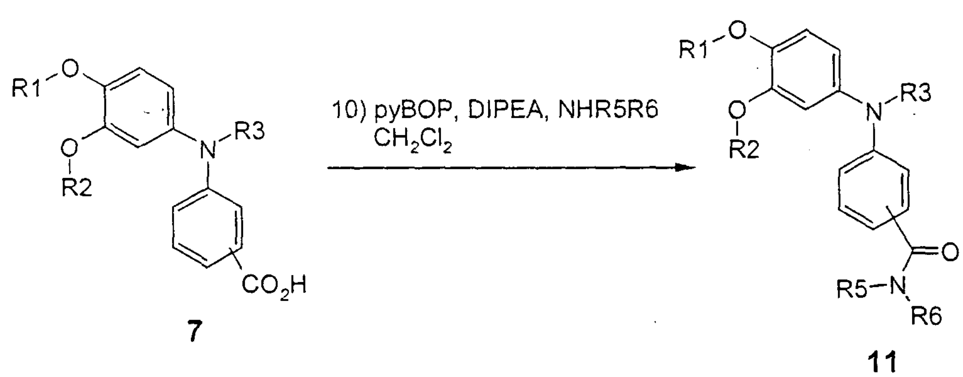


Diphenylamines **10** can be prepared by coupling appropriately substituted anilines **3**, such as 3-cyclopentyloxy-4-methoxyaniline, with arylboronic acids in the presence of a base such as triethylamine and a copper catalyst such as copper acetate (as described by Chan et al, *Tetrahedron Lett.*, 39, 2933-2936 (1998)). In general, halogenated solvents such as dichloromethane, chloroform, dichloroethane, and the like as well as nonpolar aprotic solvents such as benzene, toluene, or xylene are utilized. Such diphenylamines (e.g., **10**) can more preferably be synthesized by metal catalyzed amination reactions. For example, reaction of an appropriately substituted aniline **3** with an arylhalide in the presence of a base (e.g., K_3PO_4,

$CsCO_3$, or NaOtBu) and a palladium or nickel catalyst, for example Pd(dppf)Cl_2, a ligand (e.g., dppf) and a base (e.g., NaOtBu) (*JACS.* 1996, *118*, 7217) or with Pd_2dba_3, a bulky electron rich phosphine such as $P(tBu)_3$, and a base (e.g., NaOtBu) (*J. Org. Chem.* 1999, *64*, 5575) provides the desired diphenylamines **10**. Solvents most commonly utilized in this type of reaction include non-polar aprotic solvents such as benzene, toluene, tetrahydrofuran, ether, and the like.

Diphenylamines **10** can then be alkylated with various alkyl halides or arylalkyl halides such as, but not limited to iodomethane, ethylbromide, benzylchloride, 3-(chloromethyl)pyridine, 4-(chloromethyl)-2,6-dichloropyridine, and 4-(bromomethyl)-benzoic acid, or salts thereof, in the presence of a non-nucleophilic base such as sodium hydride, potassium hexamethyldisilazide or potassium diisopropylamide to provide *N*-substituted diphenylamines **5**. Solvents useful in this reaction include aprotic solvents such as benzene, toluene, tetrahydrofuran, ether, DMF, and the like.

SCHEME 5



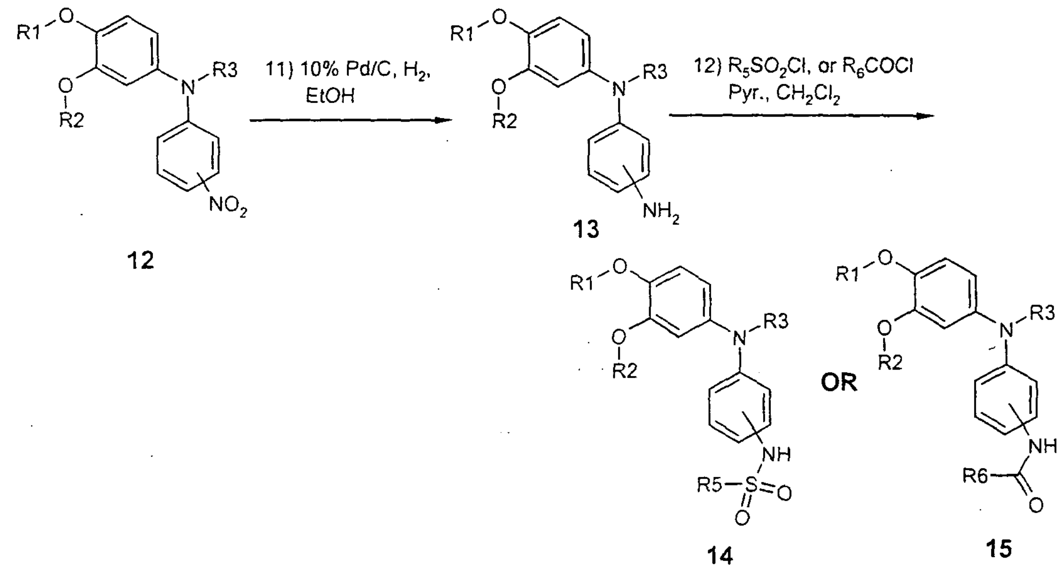
Carboxylic acids **7** can be further manipulated to form carboxamides **11** using methods standard in the art. For example, a carboxylic acid can be treated with a suitable primary or secondary amine, in the presence of a suitable coupling reagent such as BOP, pyBOP or DCC,

and a base such as Et_3N or DIEA to yield a carboxamide. These reactions generally take place in non-polar aprotic solvents such as dichloromethane, chloroform, or dichloroethane.

Carboxylic esters **6** or acids **7** can be reduced using methods standard in the art to give the corresponding carboxaldehyde or hydroxymethyl analogs. For example, an aryl ethyl ester (e.g., structure **6**, R5 = ethyl) can be treated with an appropriate reducing agent (e.g., LAH, DIBAL, etc.) in an aprotic solvent such as ether or THF, to produce the corresponding carboxaldehydes or hydroxymethyl analogs. Such aldehydes and alcohols can be further derivatised by methods standard in the art.

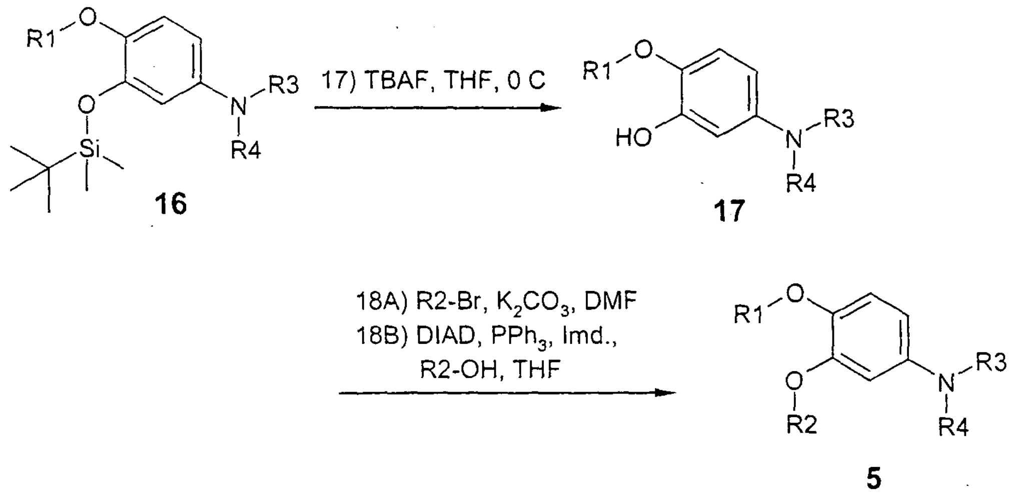
Similarly carboxamides (e.g., structure **11**) and nitriles can be reduced using methods standard in the art to provide the corresponding substituted amines or aminomethyl analogs. For example, an aryl carboxamide **11** can be reduced with an appropriate reducing agent (e.g., LAH) in an aprotic solvent (e.g., benzene, toluene, ether, THF, etc.) to give the corresponding substituted aminomethyl analog. Whereas reduction of an aryl nitrile yields the corresponding primary aminomethyl analog.

SCHEME 6



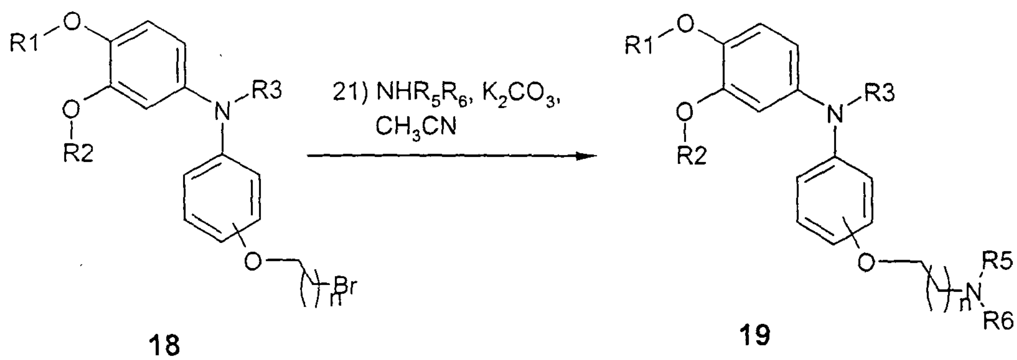
Nitrobenzene compounds **12** can be reduced to the corresponding anilines **13** by methods standard in the art such as hydrogenation using a suitable catalyst (e.g., Pd on carbon) in a polar protic solvent (e.g., EtOH, MeOH, etc.). Nitrobenzenes **12** can also be reduced using a hydride source (e.g., $NaBH_4$) and a transition metal catalyst (e.g., $NiCl_2$, Pd on carbon) in polar protic solvents such as EtOH, to produce the corresponding anilines **13**. These anilines can then be further substituted by methods standard in the art. For example, anilines of the type **13** can be alkylated, acylated, or sulfonylated to give the corresponding *N*-alkyl amines, carboxamides (e.g., structure **15**) or sulfonamides (e.g., structure **14**) respectively. For example, a sulfonamide can be prepared from an aniline and an appropriate sulfonyl halide or sulfonic anhydride (e.g., $MeSO_2Cl$, $EtSO_2Cl$, $BnSO_2Cl$, $PhSO_2Cl$, etc.) in the presence of a base (e.g., Et_3N, pyridine, DIEA, etc.). Suitable solvents for this reaction include non-polar aprotic solvents such as dichloromethane, chloroform, ether, and the like.

SCHEME 7



Trialkylsilylethers of the type **16** are prepared as described in **Scheme 1**. The *tert*-butyldimethylsilyl protected catechol intermediates **16** are readily deprotected by numerous literature methods (see Greene, T.W. and Wuts, P.G.M., Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1999, pp. 273-276.) such as by using a fluoride ion source (e.g., Bu_4NF) in an aprotic solvent such as ether or THF; or under acidic conditions (e.g., KF, 48% HBr, DMF). The resultant phenol **17**, which is a very useful synthetic intermediate, can then be alkylated by methods standard in the art and in a similar manner as described for the alkylation of nitrophenol **2** in **Scheme 1**. For example, by the Mitsunobu reaction, by reaction with an alkyl halide in the presence of a base, or by Ullman type aryl coupling or by reaction with vinyl-, aryl- or heteroaryl- boronic acids in the presence of a copper catalyst.

SCHEME 8



Haloalkoxy intermediates **18**, prepared by alkylation of the corresponding phenol, can be alkylated by reactions with substituted amines, alcohols, or thiols in the presence of a base to provide analogs such as **19**. For example, an alkyl halide can be aminated with an appropriate primary or secondary amine and a base such as K_2CO_3, in a polar aprotic solvent such as THF, DMF, or CH_3CN.

Many of these synthetic procedures are described more fully in the examples below.

One of ordinary skill in the art will recognize that some of the compounds of Formula (I) and the specific compounds listed above can exist in different geometrical isomeric forms. In addition, some of the compounds of the present invention possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers, as well as in the form of racemic or nonracemic mixtures thereof, and in the form of diastereomers and diastereomeric mixtures inter alia. All of these compounds, including cis isomers, trans isomers, diastereomic mixtures, racemates, nonracemic mixtures of enantiomers, and substantially pure and pure enantiomers, are within the scope of the present invention. Substantially pure enantiomers contain no more than 5% w/w of the corresponding opposite enantiomer, preferably no more than 2%, most preferably no more than 1%.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivation, optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivitization, are also useful. The optically active compounds of Formula I and the specific compounds listed above can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In addition, one of ordinary skill in the art will recognize that the compounds can be used in different enriched isotopic forms, e.g., enriched in the content of 2H, 3H, 11C and/or 14C.

The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts and prodrugs of all the compounds of the present invention. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable

salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, mangnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The following are further examples of acid salts that can be obtained by reaction with inorganic or organic acids: acetates, adipates, alginates, citrates, aspartates, benzoates, benzenesulfonates, bisulfates, butyrates, camphorates, digluconates, cyclopentanepropionates, dodecylsulfates, ethanesulfonates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, fumarates, hydrobromides, hydroiodides, 2-hydroxy-ethanesulfonates, lactates, maleates, methanesulfonates, nicotinates, 2-naphthalenesulfonates, oxalates, palmoates, pectinates, persulfates, 3-phenylpropionates, picrates, pivalates, propionates, succinates, tartrates, thiocyanates, tosylates, mesylates and undecanoates.

Preferably, the salts formed are pharmaceutically acceptable for administration to mammals. However, pharmaceutically unacceptable salts of the compounds are suitable as intermediates, for example, for isolating the compound as a salt and then converting the salt back to the free base compound by treatment with an alkaline reagent. The free base can then, if desired, be converted to a pharmaceutically acceptable acid addition salt.

The compounds of the invention can be administered alone or as an active ingredient of a formulation. Thus, the present invention also includes pharmaceutical compositions of

compounds of Formulae I or the compounds specifically mentioned above containing, for example, one or more pharmaceutically acceptable carriers.

Numerous standard references are available that describe procedures for preparing various formulations suitable for administering the compounds according to the invention. Examples of potential formulations and preparations are contained, for example, in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (current edition); Pharmaceutical Dosage Forms: Tablets (Lieberman, Lachman and Schwartz, editors) current edition, published by Marcel Dekker, Inc., as well as Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (current edition).

In view of their high degree of PDE4 inhibition, the compounds of the present invention can be administered to anyone requiring or desiring PDE4 inhibition, and/or enhancement of cognition. Administration may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration.

Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and excipients known in the art, including but not limited to suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the present invention.

Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable inert diluents known in the art such as water and suitable excipients known in the art such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

Suppositories for rectal administration of the compounds of the present invention can be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols. Formulations for vaginal administration can be in the form of a pessary, tampon, cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such suitable carriers as are known in the art.

For topical administration the pharmaceutical composition can be in the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

Aerosol formulations suitable for administering via inhalation also can be made. For example, for treatment of disorders of the respiratory tract, the compounds according to the invention can be administered by inhalation in the form of a powder (e.g., micronized) or in the form of atomized solutions or suspensions. The aerosol formulation can be placed into a pressurized acceptable propellant.

The compounds can be administered as the sole active agent or in combination with other pharmaceutical agents such as other agents used in the treatment of cognitive impairment and/or

in the treatment of psychosis, e.g., other PDE4 inhibitors, calcium channel blockers, chloinergic drugs, adenosine receptor modulators, amphakines NMDA-R modulators, mGluR modulators, and cholinesterase inhibitors (e.g., donepezil, rivastigimine, and glanthanamine). In such combinations, each active ingredient can be administered either in accordance with their usual dosage range or a dose below its usual dosage range.

The present invention further includes methods of treatment that involve inhibition of PDE4 enzymes. Thus, the present invention includes methods of selective inhibition of PDE4 enzymes in animals, e.g., mammals, especially humans, wherein such inhibition has a therapeutic effect, such as where such inhibition may relieve conditions involving neurological syndromes, such as the loss of memory, especially long-term memory. Such methods comprise administering to an animal in need thereof, especially a mammal, most especially a human, an inhibitory amount of a compound, alone or as part of a formulation, as disclosed herein.

The condition of memory impairment is manifested by impairment of the ability to learn new information and/or the inability to recall previously learned information. Memory impairment is a primary symptom of dementia and can also be a symptom associated with such diseases as Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, HIV, cardiovascular disease, and head trauma as well as age-related cognitive decline.

Dementias are diseases that include memory loss and additional intellectual impairment separate from memory. The present invention includes methods for treating patients suffering from memory impairment in all forms of dementia. Dementias are classified according to their cause and include: neurodegenerative dementias (e.g., Alzheimer's, Parkinson's disease, Huntington's disease, Pick's disease), vascular (e.g., infarcts, hemorrhage, cardiac disorders),

mixed vascular and Alzheimer's, bacterial meningitis, Creutzfeld-Jacob Disease, multiple sclerosis, traumatic (e.g., subdural hematoma or traumatic brain injury), infectious (e.g., HIV), genetic (down syndrome), toxic (e.g., heavy metals, alcohol, some medications), metabolic (e.g., vitamin B12 or folate deficiency), CNS hypoxia, Cushing's disease, psychiatric (e.g., depression and schizophrenia), and hydrocephalus.

The present invention includes methods for dealing with memory loss separate from dementia, including mild cognitive impairment (MCI) and age-related cognitive decline. The present invention includes methods of treatment for memory impairment as a result of disease. In another application, the invention includes methods for dealing with memory loss resulting from the use of general anesthetics, chemotherapy, radiation treatment, post-surgical trauma, and therapeutic intervention.

The compounds may be used to treat psychiatric conditions including schizophrenia, bipolar or manic depression, major depression, and drug addiction and morphine dependence. These compounds may enhance wakefulness. PDE4 inhibitors can be used to raise cAMP levels and prevent neurons from undergoing apoptosis. PDE4 inhibitors are also known to be anti-inflammatory. The combination of anti-apoptotic and anti-inflammatory properties make these compounds useful to treat neurodegeneration resulting from any disease or injury, including stroke, spinal cord injury, neurogenesis, Alzheimer's disease, multiple sclerosis, amylolaterosclerosis (ALS), and multiple systems atrophy (MSA).

Thus, in accordance with a preferred embodiment, the present invention includes methods of treating patients suffering from memory impairment due to, for example, Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, depression, aging, head trauma, stroke, CNS hypoxia, cerebral senility,

multiinfarct dementia and other neurological conditions including acute neuronal diseases, as well as HIV and cardiovascular diseases, comprising administering an effective amount of a compound according to Formula (I), or of the compounds listed above, or pharmaceutically acceptable salts thereof.

The compounds of the present invention can also be used in a method of treating patients suffering from disease states characterized by decreased NMDA function, such as schizophrenia. The compounds can also be used to treat psychosis characterized by elevated levels of PDE 4, for example, various forms of depression, such as manic depression, major depression, and depression associated with psychiatric and neurological disorders.

As mentioned, the compounds of the invention also exhibit anti-inflammatory activity. As a result, the inventive compounds are useful in the treatment of a variety of allergic and inflammatory diseases, particularly disease states characterized by decreased cyclic AMP levels and/or elevated phosphodiesterase 4 levels. Thus, in accordance with a further embodiment of the invention, there is provided a method of treating allergic and inflammatory disease states, comprising administering an effective amount of a compound according to Formula (I), or of the compounds listed above, or a pharmaceutically acceptable salt thereof. Such disease states include: asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, esoniophilic granuloma, psoriasis, inflammatory arthritis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, cystic fibrosis, arterial restenosis, artherosclerosis, keratosis, rheumatoid spondylitis, osteoarthritis, pyresis, diabetes mellitus, pneumoconiosis, chronic obstructive airways disease, chronic obstructive pulmonary disease,

toxic and allergic contact eczema, atopic eczema, seborrheic eczema, lichen simplex, sunburn, pruritis in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, systemic lupus erythematosus, follicular and wide-area pyodermias, endogenous and exogenous acne, acne rosacea, Beghet's disease, anaphylactoid purpura nephritis, inflammatory bowel disease, leukemia, multiple sclerosis, gastrointestinal diseases, autoimmune diseases and the like.

PDE4 inhibitors for treating asthma, chronic bronchitis, psoriasis, allergic rhinitis, and other inflammatory diseases, and for inhibiting tumor necrosis factor are known within the art. See, e.g., WO 98/58901, JP11-18957, JP 10-072415, WO 93/25517, WO 94/14742, US 5,814,651, and US 5,935,978. These references also describe assays for determining PDE4 inhibition activity, and methods for synthesizing such compounds. The entire disclosures of these documents are hereby incorporated by reference.

PDE4 inhibitors may be used to prevent or ameliorate osteoporosis, as an antibiotic, for treatment of cardiovascular disease by mobilizing cholesterol from atherosclerotic lesions, to treat rheumatoid arthritis (RA), for long-term inhibition of mesenchymal-cell proliferation after transplantation, for treatment of urinary obstruction secondary to benign prostatic hyperplasia, for suppression of chemotaxis and reduction of invasion of colon cancer cells, for treatment of B cell chronic lymphocytic leukemia (B-CLL), for inhibition of uterine contractions, to attenuate pulmonary vascular ischemia-reperfusion injury (IRI) , for corneal hydration , for inhibition of IL-2R expression and thereby abolishing HIV-1 DNA nuclear import into memory T cells, for augmentation of glucose-induced insulin secretion, in both the prevention and treatment of colitis, and to inhibit mast cell degranulation.

The compounds of the present invention can be administered as the sole active agent or in combination with other pharmaceutical agents such as other agents used in the treatment of

a) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

b) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-6-aminonicotinic acid

c) *N*-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-amino-2-chlorobenzoic acid (MW 454.908; ESMS *m/z* (453.5 M-H)$^-$)

d) N-3,4-bis(difluoromethoxy)phenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid

EXAMPLE 13

N-(3,4-Bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic Acid

A solution consisting of 1.75 g (3.44 mmol) of tert-butyl N-(3,4-bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate, 33.5 mL of dichloromethane and 8.4 mL of trifluoroacetic acid was stirred at room temperature for 5 hours. The solution was washed with 50 mL of H_2O. Then 50 mL of H_2O was added and the pH adjusted to 6 by the addition of 10% aqueous NaOH. The combined aqueous layers were extracted with 2 x 50 mL of dichloromethane. The combined dichloromethane extracts were evaporated and the remaining material was purified by flash chromatography over SiO_2 using 10% MeOH in CH_2Cl_2 as eluant. The material was triturated with CH_3CN to yield 1.09 g (73% yield) of the title compound as a white crystalline powder. [MW 436.359; ESMS *m/z* (M+H)$^+$]

The following compounds were prepared in a similar manner as described above:

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-amino-6-methylbenzoic acid (MW 434.489; ESMS *m/z* 435 (M+H)$^+$)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 420.463; ESMS *m/z* 421.1 (M+H)$^+$)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-4-aminobenzoic acid (MW 438.453; ESMS *m/z* 439 $(M+H)^+$)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-(1,3-dimethylpyrazolylmethyl)-3-aminobenzoic acid (MW 437.493; ESMS *m/z* 438 $(M+H)^+$)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-5-trifluoromethyl-3-aminobenzoic acid (MW 488.46; ESMS *m/z* 489 $(M+H)^+$)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-6-trifluoromethyl-3-aminobenzoic acid (MW 488.46; ESMS *m/z* 487.5 $(M-H)^-$)

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 456.443; ESMS *m/z* 455.3 $(M-H)^-$)

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-3-aminobenzoic acid (MW 436.48; ESMS *m/z* 437 $(M+H)^+$)

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-4-aminobenzoic acid (MW 436.48; ESMS *m/z* 437 $(M+H)^+$)

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 456.443; ESMS *m/z* 457.4 $(M+H)^+$)

N-(3-Cyclobutyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 404.464; ESMS *m/z* 405 $(M+H)^+$)

N-(3-Cyclohexyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 432.517; ESMS *m/z* 433 $(M+H)^+$)

N-(3-Cycloheptyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 446.544; ESMS *m/z* 447 $(M+H)^+$)

N-(4-Methoxy-3-(4-pyranyloxy)phenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 434.489; ESMS *m/z* 435 $(M+H)^+$)

N-(3-[2.2.2-Bicyclooctanyl]oxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 444.528; ESMS *m/z* 445 $(M+H)^+$)

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(2,6-difluorobenzyl)-3-aminobenzoic acid (MW 453.483; ESMS *m/z* 454 $(M+H)^+$)

N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(4-(3,5-dimethylisoxazolyl))-3-aminobenzoic acid (MW 436.505; ESMS *m/z* 437 $(M+H)^+$)

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoic acid (MW 436.48; ESMS *m/z* 437 $(M+H)^+$)

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoic acid (MW 472.461; ESMS *m/z* 473 $(M+H)^+$)

N-(3,4-Bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoic acid (MW 454.349; ESMS *m/z* 455 $(M+H)^+$)

N-(3-Cyclobutyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 404.464; ESMS *m/z* 405 $(M+H)^+$)

N-(3-Cyclohexyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 432.517; ESMS *m/z* 433 $(M+H)^+$)

N-(4-Methoxy-3-(2-(2-Pyridylethoxy))phenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 455.512; ESMS *m/z* 456 $(M+H)^+$)

N-(3,4-Dimethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 364.399; ESMS *m/z* 365.2 $(M+H)^+$)

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 378.426; ESMS m/z 379.2 $(M+H)^+$)

N-(3-Isopropoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 392.453; ESMS m/z 393.2 $(M+H)^+$)

3,4-Bis(difluoromethoxy)-N-(3-carboxyphenyl)-N-(5-(2-chloropyridylmethyl))aniline (MW 470.805)

3,4-Bis(difluoromethoxy)-N-(3-carboxyphenyl)-N-(3-(2-chloropyridylmethyl))aniline (MW 470.805)

3,4-Bis(difluoromethoxy)-N-(3-carboxyphenyl)-N-(4-(3,5-dimethylisoxazolyl)methyl)aniline (MW 454.374)

3,4-Bis(difluoromethoxy)-N-(3-carboxyphenyl)-N-(3-(4-chloropyridylmethyl))aniline (MW 470.805)

3,4-Bis(difluoromethoxy)-N-(3-carboxy-4-chlorophenyl)-N-(3-pyridylmethyl))aniline (MW 470.805)

3,4-Bis(difluoromethoxy)-N-(3-carboxyphenyl)-N-(3-(4-methoxypyridylmethyl))aniline (MW 466.385)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(3-(4-chloropyridylmethyl))aniline (MW 452.935)

3,4-Bis(difluoromethoxy)-N-(3-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline (MW 505.25)

3-Cyclopentyloxy-4-hydroxy-N-(3-carboxyphenyl)-N-(3-pyridylmethyl)aniline (MW 404.464)

4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-(3-carboxy-4-chlorophenyl)-N-(3-pyridylmethyl)aniline (MW 454.908)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxyphenyl)-N-(4-(3-chloropyridylmethyl))aniline (MW 452.935)

4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-(3-carboxyphenyl)-N-(4-pyridylmethyl)aniline (MW 420.463)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(4-pyridylmethyl)aniline (MW 418.49)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxy-3-chlorophenyl)-N-(3-pyridylmethyl)aniline (MW 452.935)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxy-3-methylphenyl)-N-(3-pyridylmethyl)aniline (MW 432.517)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxy-3-fluorophenyl)-N-(3-pyridylmethyl)aniline (MW 436.48)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-chlorophenyl)-N-(3-pyridylmethyl)aniline (MW 452.935)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-fluorophenyl)-N-(3-pyridylmethyl)aniline (MW 436.48)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline (MW 487.381)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline (MW 487.381)

3-Cyclopentyloxy-4-methoxy-N-(4-carboxyphenyl)-N-(4-(3-chloropyridylmethyl))aniline (MW 452.935)

4-Methoxy-3-(3R)-tetrahydrofuryloxy-N-(4-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline (MW 489.353)

4-Methoxy-3-(3R)-tetrahydrofuryloxy-N-(3-carboxyphenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline (MW 489.353)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-methoxyphenyl)-N-(3-pyridylmethyl)aniline (MW 448.516)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-methylphenyl)-N-(3-pyridylmethyl)aniline (MW 432.517)

3-Cyclopentyloxy-4-methoxy-N-(3-carboxy-4-nitrophenyl)-N-(3-pyridylmethyl)aniline (MW 463.487)

N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 404.464; ESMS, m/z 405.2 (M+H)+)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-chloro-3-pyridylmethyl)-3-aminobenzoic acid (MW 454.908; ESMS, m/z 455, 457 $(M+H)^+$)

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-fluorobenzyl)-4-aminobenzoic acid (MW 437.465; ESMS, m/z 438.1 $(M+H)^+$)

N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (MW 454.471; ESMS, m/z 455.1 $(M+H)^+$)

N-(3,4-Dimethoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 364.399; ESMS, m/z 365.2 $(M+H)^+$)

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 378.426; ESMS, m/z 379.2 $(M+H)^+$)

N-[4-Methoxy-3-(1-propyl)oxyphenyl]-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 392.453; ESMS, m/z 393.2 $(M+H)^+$)

N-[4-Methoxy-3-(2-propyl)oxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 392.453; ESMS, m/z 393.2 $(M+H)^+$)

N-(3-Cyclopropylethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 418.49; ESMS, m/z 419.2 $(M+H)^+$)

N-(3-Cyclobutylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 418.49; ESMS, m/z 419.2 $(M+H)^+$).

EXAMPLE 14A

3-(tert-Butyldimethylsilyloxy)cyclopentanol

Sodium Hydride (3.77 g, 0.094 mol, 60 % in mineral oil) was added to a solution of 1,3-cyclopentanediol (9.62 g, 0.094 mol) in 100 mL of THF. A slight generation of gas was observed. After stirring at room temperature for 1 h, tert-butyldimethylsilyl chloride (14.2 g, 0.094 mol) was added and the mixture was stirred at room temperature over night. The reaction mixture was diluted with 500 mL of ethyl acetate and washed with 125 mL of 10% K_2CO_3, brine, and dried over Na_2SO_4. The solution was concentrated and dried in vacuo to give 20.3 g of crude product as a colorless oil. Further purification over SiO_2 using a gradient elution 5% EtOAc/hexanes to 10% EtOAc/hexanes provided the desired compound as a colorless oil (7.1 g, 35 % yield).

EXAMPLE 14B

3-(tert-Butyldimethylsilyloxy)-1-(4-toluenesulfonyloxy)cyclopentane

3-(tert-Butyldimethylsilyloxy)cyclopentanol (4.8 g, 0.022mol) and 4.22 g (0.022 mol) of tosyl chloride were mixed with 45 mL of pyridine and stirred at room temperature over night. TLC revealed the completion of the reaction. The pyridine was removed in vacuo and the residue

was dissolved in ethyl acetate, washed with 1 N HCl and brine, and dried over Na_2SO_4. The filtrate was concentrated under vacuum to dryness to obtain 8.0 g of crude desired product as a light pink residue. The crude product was purified over SiO_2 using 3% EtOAc in hexanes as eluant to give two lots material. The first lot contained 2.50 g of product approximately 90 % pure. The second lot contained 2.66 g of desired product with greater than 98% purity. The combined yield was approximately 60 %.

EXAMPLE 14C

Methyl N-(3-(3-tert-butyldimethylsilyloxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

3-(tert-Butyldimethylsilyloxy)-1-(4-toluenesulfonyloxy)cyclopentane (2.33 g, 6.28 mmol) was added to a solution of 1.76 g (4.83 mmol) of methyl N-(3-(3-hydroxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate in 20 mL of N,N dimethylformamide. NaH (0.231 g, 5.80 mmol, 60 % in mineral oil) was added to the reaction mixture and then warmed to 75°C under nitrogen over night with stirring. TLC revealed the completion of the reaction. The DMF was removed in vacuo and the residue was dissolved in ethyl acetate, washed with saturated NH_4Cl and brine, dried over Na_2SO_4. The filtrate was concentrated under vacuum to dryness to obtain 4.3 g crude desired product as a residue. The crude product was purified by flash silica gel chromatography using a gradient elution from 15% EtOAc in hexanes to 20% EtOAc in hexanes. The desired compound was obtained as a dark orange oil (1.3 g, 48 % yield).

EXAMPLE 14D

Methyl N-(3-(3-Hydroxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

2 N HCl (3 mL) was added to a solution of 1.3 g (2.3 mmol) of methyl N-(3-(3-tert-butyldimethylsilyloxy)-cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate in 60 mL of MeOH and stirred at room temperature for 2 hour. The solvent was concentrated in vacuo and the residue dissolved in ethyl acetate, washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. The filtrate was concentrated under vacuum to dryness to obtain 1.0 g crude desired product as a light brown foaming solid. The crude product was purified by flash silica gel chromatography (2M NH_3 in MeOH: CH_2Cl_2 = 1.5: 98.5), the desired compound was obtained as pale yellow foaming solid (695 mg, 67 %) which was confirmed by ^{1}H NMR and Mass.

EXAMPLE 15A

t-Butyl N-(2-(3-pyridyl)ethy)l-3-aminobenzoate

To a mixture of 244 mg of 3-(2-aminoethyl)pyridine (2.0 mmol) and 604 mg of *t*-butyl 3-iodobenzoate (2.0 mmol) in 10 mL of toluene was added 250 mg of sodium *t*-butoxide (2.5 mmol), 30 mg of tri-*t*-butylphosphonium tetrafluoroborate (0.1 mmol) and 50 mg of tris(dibenzylidineacetone)dipalladium(0) (0.055 mmol). The mixture was stirred for 16 h and filtered through celite. The celite was washed with 3 X 5 mL of toluene and the filtrate was concentrated in vacuo. The residue was purified by column chromatography using 35%-45% EtOAc in hexanes as eluant to give 103 mg of *t*-butyl N-(2-(3-pyridyl)ethyl)-3-aminobenzoate as a bright yellow oil (17% yield).

EXAMPLE 15B

t-Butyl N-(3-cyclopentyloxy-4-methoxyphenyl)-N-(2-(3-pyridyl)ethyl)-3-aminobenzoate

To a mixture of 103 mg of t-butyl N-(2-(3-pyridyl)ethyl)-3-aminobenzoate (0.35 mmol) and 200 mg of 3-cyclopentyloxy-4-methoxyiodobenzene (0.63 mmol) in 5 mL of toluene was added 100 mg of sodium t-butoxide (1.0 mmol), 15 mg of tri-t-butylphosphonium tetrafluoroborate (0.05 mmol) and 25 mg of tris(dibenzylidineacetone)dipalladium(0) (0.028 mmol). The mixture was stirred for 16 h and filtered through celite. The celite was washed with 3 X 5 mL of toluene and the filtrate was concentrated in vacuo. The residue was purified by column chromatography using 30%-40% EtOAc in hexanes as eluant to give 48 mg of t-butyl N-(3-cyclopentyloxy-4-methoxyphenyl)-N-(2-(3-pyridyl)ethyl)-3-aminobenzoate.

The following compounds were prepared in a similar manner as described above:

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(2-(3-pyridylethyl))-3-aminobenzoic acid (MW 432.517; ESMS m/z 433 $(M+H)^+$)

EXAMPLE 16

3-Cyclopropylmethyloxy-4-difluoromethoxy-N-(3-pyridylmethyl)-4'-(2H-tetrazol-5-yl)diphenylamine

3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3-pyridylmethyl)-4'-[2-(2-tetrahydropyranyl)-2H-tetrazol-5-yl]diphenylamine (1.5 g, 0.26 mmol) was dissolved in THF (5 mL) and 3 mL of 1N HCl was added. After 6 h at room temperature, the mixture was neutralized to pH = 5 with saturated aqueous sodium bicarbonate and extracted with EtOAc (3 x 50 mL). The EtOAc extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was loaded onto a RediSep column (10 g, silica gel) and the product was eluted using a linear gradient from 0% MeOH in EtOAc to 5% MeOH in EtOAc over 20 min to give 0.96 g of product as a white powder. ^{1}H NMR (CD_3OD) δ 8.55 (s,

1H), 8.43 (d, 1H, J = 4.9 Hz), 7.65 (d, 1H, 8.0 Hz), 7.21 (dd, 1H, J = 4.9 Hz, 8.0 Hz), 7.18 (d, 1H, J = 8.9 Hz), 7.10-6.90 (m, 3H), 6.87 (dd, 1H, J = 8.6 Hz, 2.5 Hz), 6.75 (t, 1H, J = 75.5 Hz), 5.14 (s, 2H), 3.82 (d, 2H, J = 6.9 Hz), 1.23 (m, 1H), 0.60 (m, 2H), 0.33 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-4'-(2H-tetrazol-5-yl)diphenylamine

b) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-3'-(2H-tetrazol-5-yl)diphenylamine

c) 4-Methoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)-4'-(2H-tetrazol-5-yl)diphenylamine

d) 3-Cyclopropylmethyloxy-4-methoxy-*N*-(3-pyridylmethyl)-4'-(2H-tetrazol-5-yl)diphenylamine

e) 4-Difluoromethoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)-4'-(2H-tetrazol-5-yl)diphenylamine

f) 3-Cyclopentyloxy-4-difluromethoxy-*N*-(3-pyridylmethyl)-4'-(2H-tetrazol-5-yl)diphenylamine

g) 3-Cyclopropylmethyloxy-4-difluoromethoxy-*N*-(3-pyridylmethyl)-3'-(2H-tetrazol-5-yl)diphenylamine

h) Bis-3,4-difluoromethoxy-*N*-(3-pyridylmethyl)-4'-(2H-tetrazol-5-yl)diphenylamine

i) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-chloro-4-(5-(2H)-tetrazolyl)aniline (MW 478.938; ESMS *m/z* 479.0, 481.0 $(M+H)^+$)

j) N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-chloro-4-(5-(2H)-tetrazolyl)aniline (MW 476.966; ESMS *m/z* 477.0, 478.9 $(M+H)^+$)

k) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridyl)methyl)-4-(5-(2H)-tetrazolyl)aniline (MW 513.383; ESMS *m/z* 513, 515, 517 $(M+H)^+$), and

l) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-piperidinyl)sulfonylaniline, (MW 523.651; ESMS m/z 524 (M+H)+)

EXAMPLE 17 (Method A)

3-Cyclopentyloxy-4-methoxydiphenylamine

Method A. (Ref. Chan, D.M.T.; Monaco, K.L.; Wang, R.P.; Winters, M.P., *Tetrahedron Lett.*, 1998, *39*, 2933-2936.). A slurry of 207 mg of 4-methoxy-3-cyclopentyloxyaniline, 280 mg of phenylboronic acid, 182 mg of $Cu(OAc)_2$, 280 μL of Et_3N and 4.0 mL of CH_2Cl_2 was stirred for 20 h at room temp. The black mixture was filtered through silica eluting with CH_2Cl_2, concentrated, and purified by chromatoghraphy over SiO_2 using EtOAc/Hexanes (15/85) as eluant to provide 75 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.26-7.20 (m, 2H), 6.94-6.63 (m, 6H), 5.50 (s, 1H), 4.71 (m, 1H), 3.82 (s, 3H), 1.89-1.54 (m, 8H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-3',4-dimethoxydiphenylamine

b) 3'-Chloro-3-cyclopentyloxy-4-methoxydiphenylamine

c) 3-Cyclopentyloxy-4-methoxy-3'methyldiphenylamine

d) 3-Cyclopentyloxy-4'-fluoro-4-methoxydiphenylamine

e) 3-Cyclopentyloxy-4-methoxy-4'-vinyldiphenylamine

f) 3'-Cyano-3-cyclopentyloxy-4-methoxydiphenylamine

g) 4'-Chloro-3-cyclopentyloxy-4-methoxydiphenylamine

h) 3-Cyclopentyloxy-4,4'-dimethoxydiphenylamine

i) 3-Cyclopentyloxy-4-methoxy-2'-methyldiphenylamine

j) 3-Cyclopentyloxy-4-methoxy-4'-methyldiphenylamine

k) 2'-Chloro-3-cyclopentyloxy-4-methoxydiphenylamine

l) 3-Cyclopentyloxy-2',4-dimethoxydiphenylamine

m) 3-Cyclopentyloxy-4-methoxy-3'-trifluoromethyldiphenylamine

n) 3-Cyclopentyloxy-4-methoxy-4'-trifluoromethyldiphenylamine

o) 3-Cyclopentyloxy-2',5'-dimethyl-4-methoxydiphenylamine

EXAMPLE 17 (Method B)

3-Cyclopentyloxy-4-methoxydiphenylamine

Method B (*Angew. Chem. Int. Ed.*, 1995, *34*(17), 1348-1351.) A mixture of 207 mg of 3-cyclopentyloxy-4-methoxyaniline, 204 mg of iodobenzene, 115 mg of NaOtBu, 9 mg of $Pd_2(dba)_3$, 12 mg of $P(o\text{-tol})_3$ and 7 mL of toluene was combined and warmed with stirring to 100°C for 4h. The mixture was cooled to room temp, diluted with 25 mL of EtOAc and washed with 10 mL of H_2O, 10 mL of brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography over SiO_2 using EtOAc/hexanes (5/95) as eluant to provide 84 mg of the desired product.

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-methoxy-2',4'-dimethyldiphenylamine

b) 3-Cyclopentyloxy-2',5'-dimethyl-4-methoxydiphenylamine

c) 3-Cyclopentyloxy-2',3'-dimethyl-4-methoxydiphenylamine

d) 3-Cyclopentyloxy-3',4'-dimethyl-4-methoxydiphenylamine

e) 3-Cyclopentyloxy-3',4'-methylenedioxydiphenylamine

f) 4'-*tert*-Butyl-3-cyclopentyloxy-4-methoxydiphenylamine

g) 3-Cyclopentyloxy-3',4'-dichloro-4-methoxydiphenylamine

h) 3-Cyclopentyloxy-2',3'-dichloro-4-methoxydiphenylamine

EXAMPLE 17 (Method C)

3-Cyclopentyloxy-2',4,5'-trimethoxydiphenylamine

Method C. To a mixture of Pd(dppf)Cl_2 (0.025 mmol, 5mol%), dppf (0.075 mmol, 3dppf/Pd) and NaOtBu (0.70 mmol, 1.4 equivalents) and 1.0 mL THF was added 1-bromo-2,5-dimethoxybenzene (0.55 mmol, 1.1 equivalents) followed by 1.0 mL of a 0.5*M* solution of 3-cyclopentyloxy-4-methoxyaniline in THF. The mixture was heated to 60°C for 3 hours and diluted with ether and washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography over silica gel (Biotage Flash 12) eluting with 15% EtOAc in hexanes.

The following compounds were prepared in a similar manner as described above:

a) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-3-pyridylamine

b) 3-Cyclopentyloxy-2',4',4-trimethoxydiphenylamine

c) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyridylamine

d) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-8-quinolinylamine

e) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-2-naphthylamine

f) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-1-naphthylamine

g) 3-Cyclopentyloxy-4'-ethyl-4-methoxydiphenylamine

h) 3-Cyclopentyloxy-2'-fluoro-4-methoxy-5'-methyldiphenylamine

i) 3-Cyclopentyloxy-3'-fluoro-4-methoxy-4'-methyldiphenylamine

j) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrimidinylamine

k) 3-Cyclopentyloxy-3',5'-dichloro-4-methoxydiphenylamine

l) 3-Cyclopentyloxy-2'-ethyl-4-methoxydiphenylamine

m) 4'-Chloro-3-cyclopentyloxy-3'-fluoro-4-methoxydiphenylamine

n) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-4-isoquinolinylamine

o) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrazinylamine

p) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-5-pyrimidinylamine

q) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-1-isoquinolinylamine

r) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-3-quinolinylamine

s) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-4-pyridylamine

t) *N*-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-3-pyridylamine

u) *N*-(3-Cyclopropylmethyloxy-4-methoxyphenyl)-3-pyridylamine

v) *N*-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenyl)-3-pyridylamine

w) *N*-(4-Methoxy-3-(3*R*)-tetrahydrofuryloxyphenyl)-3-pyridylamine

x) *N*-(4-Difluoromethoxy-3-(3*R*)-tetrahydrofuryloxyphenyl)-3-pyridylamine

y) Ethyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-3-aminobenzoate

z) 3-Cyclopentyloxy-4'-(*N*,*N*-dimethylamino)-4-methoxydiphenylamine

aa) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(6-methoxypyridyl)amine

bb) Methyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-2-aminonicotinate

cc) *tert*-Butyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-6-aminonicotinate

dd) 2'-Amino-3-cyclopentyloxy-4-methoxydiphenylamine

ee) 3-Cyclopentyloxy-4-methoxy-3'-(1-phthalimido)diphenylamine

ff) 3-Cyclopentyloxy-4-methoxy-3'-[2-(2-tetrahydropyranyl)-2H-tetrazol-5-yl]diphenylamine

EXAMPLE 18 (Method A)

3-Cyclopentyloxy-4-methoxy- *N*-methyldiphenylamine

To a solution of 3-cyclopentyloxy-4-methoxydiphenylamine (70 mg, 0.25 mmol) in 3 mL of THF at 0°C was added 0.55 mL of 0.5 M $KN(TMS)_2$ in toluene. The solution was stirred at 0°C for 0.5 h and 2.0 equivalents of iodomethane was added and the reaction mixture was warmed to room temperature. Upon reaction completion as indicated by TLC, 10 mL of EtOAc was added and the mixture was washed with 3 mL of H_2O, 3 mL of brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (Biotage flash 12) using 5% EtOAc in hexanes as eluant.

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-*N*-ethyl-4-methoxydiphenylamine

b) 3-Cyclopentyloxy-4-methoxy-*N*-(1-propyl)diphenylamine

c) 3-Cyclopentyloxy-4-methoxy-*N*-[1-(3-phenpropyl)]diphenylamine

d) *N*-Benzyl-3-cyclopentyloxy-4-methoxydiphenylamine

e) 3-Cyclopentyloxy-4-methoxy-*N*-(4-pyridylmethyl)diphenylamine

f) 3-Cyclopentyloxy-4-methoxy-*N*-(2-pyridylmethyl)diphenylamine

g) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

h) 3-Cyclopentyloxy-4-methoxy-*N*-[3-(3-pyridyl)-1-propyl]diphenylamine

i) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-ethyl-4-isoquinolinylamine

j) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-benzyl-4-isoquinolinylamine

k) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-methyl-4-isoquinolinylamine

l) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-propyl-4-isoquinolinylamine

m) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(4-isoquinolinyl)-*N*-(4-pyridylmethyl)amine

n) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(4-isoquinolinyl)-*N*-(3-pyridylmethyl)amine

o) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-*N*-(5-pyrimidinyl)amine

p) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(2-pyrazinyl)-*N*-(3-pyridylmethyl)amine

q) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(2-pyridyl)-*N*-(3-pyridylmethyl)amine

r) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridyl)-*N*-(3-pyridylmethyl)amine

s) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(4-pyridyl)-*N*-(3-pyridylmethyl)amine

t) *tert*-Butyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-6-aminonicotinate

u) *N*-(3-Cyclopropylmethoxy-4-methoxyphenyl)-*N*-(3-pyridyl)-*N*-(3-pyridylmethyl)amine

v) *N*-(4-Methoxy-3-(3*R*)-tetrahydrofuryloxyphenyl)-*N*-(3-pyridyl)-*N*-(3-pyridylmethyl)amine

w) *N*-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-*N*-(3-pyridyl)-*N*-(3-pyridylmethyl)amine

x) *N*-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-*N*-(3-pyridyl)-*N*-(3-pyridylmethyl)amine

y) *N*-(4-Difluoromethoxy-3-(3*R*)-tetrahydrofuryloxyphenyl)-*N*-(3-pyridyl)-*N*-(3-pyridylmethyl)amine

z) *N*-(4-Chloro-3-pyridylmethyl)-*N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(2-pyridyl)amine

aa) *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(4-methyl-3-pyridylmethyl)-*N*-(2-pyridyl)amine

bb) 3-Cyclopentyloxy-4-methoxy-*N*-(2-thiazolylmethyl)diphenylamine

cc) *N*-(2-Chloro-3-pyridylmethyl)-3-cyclopentyloxy-4-methoxydiphenylamine

dd) *N*-(6-Chloro-3-pyridylmethyl)-3-cyclopentyloxy-4-methoxydiphenylamine

EXAMPLE 18 (Method B)

***N*-4-Chloro-3-pyridylmethyl)-*N*-(3-cyclopentyl-4-methoxyphenyl)-*N*-(2-pyridyl)amine**

To a solution of (3-cyclopentyloxy-4-methoxyphenyl)-2-pyridylamine (30 mg, 0.10 mmol) and 4-chloropicolyl chloride hydrochloride (50 mg, 0.25 mmol) was dissolved in DMF (1 mL) and sodium hydride (50 mg of a 60% mineral oil dispersion, 1.3 mmol) was added in small portions. After stirring for 1h at room temperature, the mixture was poured into 25 mL ice water. The mixture was extracted with EtOAc (2 x 15 mL) and the EtOAc extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was loaded onto a RediSep column (4.2 g, silica gel) and the product was eluted with 15% EtOAc in hexanes to give 20 mg of product as a yellow crystalline solid. ^1H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.34 (d, 1H, J = 5.3 Hz), 8.17 (d, 1H, 5.0 Hz), 7.33 (m, 1H), 7.25 (m, 1H), 6.83 (d, 1H, J = 8.5), 6.75 (d, 1H, J = 8.5), 6.71 (s, 1H), 6.62 (m, 1H), 6.42 (d, 1H, J = 8.6), 5.31 (s, 2H), 4.63 (p, 1H, J = 4.12 Hz), 3.83 (s, 3H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3,4-Bis(difluoromethoxy)-*N*-(4-chloro-3-pyridylmethyl)-3'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)diphenylamine

b) 3,4-Bis(difluoromethoxy)-*N*-(4-methyl-3-pyridylmethyl)-3'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)diphenylamine

c) 3,4-Bis(difluoromethoxy)-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(5-(2-chloropyridylmethyl))aniline

d) 3,4-Bis(difluoromethoxy)-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-(2-chloropyridylmethyl))aniline

e) 3,4-Bis(difluoromethoxy)-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3,5-dimethylisoxazolyl)methyl)aniline

f) 3,4-Bis(difluoromethoxy)-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-(4-chloropyridylmethyl))aniline

g) 3-Cyclopentyloxy-4-methoxy-N-(4-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-(4-chloropyridylmethyl))aniline

h) 3,4-Bis(difluoromethoxy)-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline.

EXAMPLE 19

3-Cyclopentyloxy-4-methoxyanilino-*N*-(3-pyridylmethyl)-*N*-3-(4-pyridyl)benzamide

To a solution of *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid (20 mg, 0.05 mmol) and pyBOP (40 mg. 0.08 mmol) in CH_2Cl_2 (2 mL) at room temperature was added diisopropylethylamine (20 μL, 0.11 mmol). After stirring for 15 min, 4-aminopyridine (15 mg, 0.15 mmol) was added and the mixture was allowed to stir 16 h. The mixture was diluted with EtOAc (25 mL) and washed with water (2 x 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was loaded onto a RediSep column (4.2 g, silica gel) and the product was eluted with a linear gradient from 40% EtOAc in hexanes to 60% EtOAc in hexanes over 15 min to give 22 mg of product. ^1H NMR ($CDCl_3$) δ 8.70-8.40 (m, 3H), 8.24 (s, 1H), 7.72 (d, 1H, 9.0 Hz), 7.68-7.55 (m, 2H), 7.30-7.20 (m, 1H), 6.88

(d, 2H, J = 8.5), 6.80-6.65 (m, 3H), 4.98 (s, 2H), 4.66 (p, 1H, J = 4.1 Hz), 3.86 (s, 3H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-(3-Cyclopentyloxy-4-methoxyanilino)-*N*-(3-pyridylmethyl)-*N*-*3*-[3-(*N*,*N*-dimethylamino)prop-1-yl]benzamide

b) 3-Cyclopentyloxy-4-methoxy-3'-(4-methylpiperazin-1-ylcarbonyl)-*N*-(3-pyridylmethyl)diphenylamine

c) 3-Cyclopentyloxy-4-difluoromethoxy-4'-(4-methylpiperazin-1-ylcarbonyl)-*N*-(3-pyridylmethyl)diphenylamine

d) 3-Cyclopentyloxy-4-methoxy-4'-(4-methylpiperazin-1-ylcarbonyl)-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuranyloxy)-diphenylamine

EXAMPLE 20

The following compounds were prepared in a similar fashion as described in Example 2:

a) 4'-Amino-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

b) 3'-Amino-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

c) 3'-Amino-3-cyclopropylmethoxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

d) 3'-Amino-4-methoxy-*N*-(3-pyridylmethyl)-3-[(3*R*)-tetrahydrofuryloxy]diphenylamine

EXAMPLE 21

3-Cyclopentyloxy-4'-methanesulfonylamino-4-methoxy-*N*-(3-pyridylmethyl)-diphenylamine

To a solution of 4'-amino-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-diphenylamine (47 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) at room temperature was added pyridine (20 microliters, 0.24 mmol) followed by methanesulfonyl chloride (15 microliters, 0.18 mmol) and the mixture was allowed to stand at room temperature for 16 h. The mixture was diluted with ether (50 mL) and washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by flash column chromatography (4.2 g RediSep column, silica gel) eluting with a linear gradient from 45% EtOAc in hexanes to 60% EtOAc in hexanes over 20 min to yield 41 mg of product. ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.41 (d, 1H, J = 4.8 Hz), 7.56 (d, 1H, 7.9 Hz), 7.16 (m, 1H), 6.98 (d, 2H, J = 9.0 Hz), 6.80-6.60 (m, 6H), 4.82 (s, 2H), 4.56 (p, 1H, J = 4.0 Hz), 3.75 (s, 3H), 2.86 (s, 3H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-3'-ethanesulfonylamino-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

b) 3-Cyclopentyloxy-4-methoxy-3'-(1-propanesulfonylamino)-*N*-(3-pyridylmethyl)diphenylamine

c) 3'-(1-Butanesulfonylamino)-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

d) 3'-Benzylsulfonylamino-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

e) 3'-Acetamido-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

f) 3-Cyclopentyloxy-4'-ethanesulfonylamino-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

g) 3-Cyclopentyloxy-4-methoxy-4'-(1-propanesulfonylamino)-*N*-(3-pyridylmethyl)diphenylamine

h) 3-Cyclopropylmethoxy-3'-ethanesulfonylamino-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

i) 4-Difluoromethoxy-3'-ethanesulfonylamino-*N*-(3-pyridylmethyl)-3-[(3R)-tetrahydrofuryloxy]diphenylamine

EXAMPLE 22

3-Cyclopentyloxy-4-methoxy-3'-hydroxymethyl-*N*-(3-pyridylmethyl)diphenylamine

To a solution of Ethyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate (50 mg, 0.11 mmol) in THF (5 mL) at 0 ^{0}C was added drop-wise, with stirring, 2.5M diisobutylaluminum hydride in toluene (0.4 mL, 1.00 mmol). The mixture was stirred at 0°C for 1 h and the excess diisobutylaluminum hydride was quenched by adding 5 drops of EtOAc to the mixture. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by flash column chromatography (4.2 g RediSep column, silica gel) eluting with 300 mL 50% EtOAc in hexanes then 100% EtOAc to give 15 mg of product. ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.40 (br, 1H), 7.58 (d, 1H, 7.9 Hz), 7.25-7.05 (m, 3H), 6.80-6.60 (m, 5H), 4.85 (s, 2H), 4.56 (p, 1H, J = 4.1 Hz), 4.50 (s, 2H), 3.76 (s, 3H), 1.86-1.70 (m, 7H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-methoxy-4'-hydroxymethyl-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 23

3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-4'-(2H-tetrazol-5-yl)diphenylamine

To a solution of *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzonitrile (100 mg, 0.25 mmol) in DMF (3 mL) was added NaN_3 (163 mg, 2.5 mmol) and NH_4Cl (135 mg, 2.5 mmol) and the mixture was stirred at 120 ^{0}C for 6 h. The mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (2 x 25 mL). The EtOAc extracts were combined, washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was loaded onto a RediSep column (4.2 g, silica gel) and eluted with a linear gradient from 50% to 75% EtOAc in hexanes to yield 12 mg of product. ^{1}H NMR ($CDCl_3$) δ 12.50 (br, 1H), 8.64 (s, 1H), 8.54 (br, 1H), 7.86 (d, 2H, J = 8.8 Hz), 7.75 (d, 1H, 7.8 Hz), 7.36 (m, 1H), 6.80-6.60 (m, 5H), 4.99 (s, 2H), 4.66 (p, 1H, J = 4.1 Hz), 3.84 (s, 3H), 1.86-1.70 (m, 7H), 1.65-1.45 (m, 2H).

EXAMPLE 24

3-Cyclopentyloxy-4-methoxy-4'-(4-methyl-1-piperazinylmethyl)-*N*-(3-pyridylmethyl)diphenylamine

To a solution of 3-cyclopentyloxy-4-methoxy-4'-(4-methylpiperazin-1-ylcarbonyl)dipheylamine (100 mg, 0.20 mmol) in THF (5 mL) was carefully added, with stirring, lithium aluminum hydride (50 mg, 1.3 mmol). The mixture was stirred for 15 min and a few drops of EtOAc was carefully added to quench the excess hydride. Water (50 mL) and CH_2Cl_2 (50 mL) were added and the mixtures were filtered through Celite. The CH_2Cl_2 layer was separated, washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified on an ISCO RediSep column (4.2 g, silica) eluting with a gradient from 5% MeOH in EtOAc to 15% MeOH in EtOAc to yield 60 mg of product as a light yellow oil. ^{1}H

NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.47 (d, 1H, J = 4.8 Hz), 7.65 (d, 1H, 7.9 Hz), 7.21 (dd, 1H, J = 4.8 Hz, 7.9 Hz), 7.11 (d, 2H, J = 8.6 Hz), 6.82-6.73 (m, 3H), 6.70-6.65 (m, 2H), 4.91 (s, 2H), 4.62 (p, 1H, J = 4.12 Hz), 3.82 (s, 3H), 3.41 (s, 2H), 2.75-2.20 (m, 8H), 2.27 (s, 3H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-methoxy-3'-(4-methyl-1-piperazinylmethyl)*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 25

3'-Aminomethyl-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

To a solution of *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzonitrile (50 mg, 0.12 mmol) in THF (5 mL) was carefully added, with stirring, lithium aluminum hydride (20 mg, 0.52 mmol). The mixture was stirred for 4 h and a few drops of water were carefully added to quench the excess hydride. Water (50 mL) and CH_2Cl_2 (50 mL) were added and the mixtures were filtered through Celite. The CH_2Cl_2 layer was separated, washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified on an ISCO RediSep column (4.2 g, silica) eluting with 10% MeOH in EtOAc to yield 20 mg of product. ^1H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.47 (br, 1H), 7.65 (d, 1H, 7.8 Hz), 7.26-7.10 (m, 2H), 6.90-6.65 (m, 6H), 4.94 (s, 2H), 4.63 (p, 1H, J = 4.1 Hz), 3.83 (s, 3H), 3.75 (m, 2H), 2.29 (br, 2H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

EXAMPLE 26

3-Hydroxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

To a solution of 3-(*tert*-butyldimethylsiloxy)-*N*-(3-pyridylmethyl)-4-methoxydiphenylamine (1.20 g, 2.85 mmol) in THF (40 mL) at 0°C, was added 1.0M tetrabutylammonium fluoride in THF (10 mL, 10 mmol). The mixture was stirred at 0°C for 30 min. Water (50 mL) was added and the mixture was extracted with ether (3 x 25 mL). The ether extracts were combined and washed with water (3 x 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was triturated with hexanes and collected by vacuum filtration to give 0.85 g of product. ^1H NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.46 (br, 1H), 7.67 (d, 1H, 7.8 Hz), 7.26-7.10 (m, 3H), 6.90-6.65 (m, 5H), 6.64 (dd, 1H, J = 8.6 Hz, 2.6 Hz), 6.53 (br, 1H), 4.92 (s, 2H), 3.86 (s, 3H).

The following compounds were prepared in a similar manner as described above:

a) 3'-Chloro-3-hydroxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine
b) Ethyl *N*-(3-hydroxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate
c) tert-Butyl N-(3-Hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate
d) tert-Butyl N-(3-Hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate
e) 3-Cyclopentyloxy-4-hydroxy-N-(3-(1,1-dimethylethoxy)carbonylphenyl)-N-(3-pyridylmethyl)aniline (MW 460.571)

EXAMPLE 27 (Method B)

The following compounds were prepared in a similar manner as described in Example 1B:

a) 3-[3-(4-Chlorophenyl)prop-1-yloxy]-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine
b) 3-[2-(4-Chlorophenyl)ethoxy]-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine
c) 4-Methoxy-3-(4-phenoxybut-1-yl)oxy-*N*-(3-pyridylmethyl)diphenylamine
d) 4-Methoxy-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

e) 4-Methoxy-3-[3-(4-methoxyphenyl)prop-1-yl]oxy-*N*-(3-pyridylmethyl)diphenylamine

f) 4-Methoxy-3-[3-(4-pyridyl)prop-1-yl]oxy-*N*-(3-pyridylmethyl)diphenylamine

g) 4-Methoxy-3-[2-(4-methoxyphenyl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

h) 4-Methoxy-3-(4-phenylbut-1-yl)oxy-*N*-(3-pyridylmethyl)diphenylamine

i) 4-Methoxy-3-[4-(4-methoxyphenyl)but-1-yl]oxy-*N*-(3-pyridylmethyl)diphenylamine

j) 4-Methoxy-3-[4-(4-nitrophenyl)but-1-yl]oxy-*N*-(3-pyridylmethyl)diphenylamine

k) 4-Methoxy-3-[2-(2-pyridyl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

l) 4-Methoxy-3-[2-(4-pyridyl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

m) 4-Methoxy-3-[3-(2-pyridyl)prop-1-yl]oxy-*N*-(3-pyridylmethyl)diphenylamine

n) 4-Methoxy-3-(2-methoxyethoxy)-*N*-(3-pyridylmethyl)diphenylamine

o) 3-Cyclopropylmethoxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

p) 4-Methoxy-3-(1-methylpyrrolidin-3-yl)oxy-*N*-(3-pyridylmethyl)diphenylamine

q) 4-Methoxy-3-(1-methylpiperidin-4-yl)oxy-*N*-(3-pyridylmethyl)diphenylamine

r) 4-Methoxy-*N*-(3-pyridylmethyl)-3-[(3*S*)-tetrahydrofuryloxy]diphenylamine

s) 4-Methoxy-*N*-(3-pyridylmethyl)-3-[(3*R*)-tetrahydrofuryloxy]diphenylamine

t) 3'-Chloro-4-methoxy-3-[2-(2-pyridyl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

u) 3'-Chloro-4-methoxy-3-[2-(4-pyridyl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

v) 3'-Chloro-4-methoxy-3-(2-methoxyethoxy)-*N*-(3-pyridylmethyl)diphenylamine

w) 3'-Chloro-4-methoxy-*N*-(3-pyridylmethyl)-3-[(3*R*)-tetrahydrofuryloxy]diphenylamine

x) 3-Cyclohexyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

y) 3-Cycloheptyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

z) 3-(2-Cyclopropylethoxy)-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

aa) 3-Cyclopentylmethoxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

bb) Ethyl *N*-[3-(4-chlorophenyl)prop-1-yloxy-4-methoxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoate

cc) Ethyl *N*-(3-cyclopropylmethoxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

dd) Ethyl *N*-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

ee) Ethyl *N*-[3-(2-indanyloxy)-4-methoxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoate

ff) Ethyl *N*-[4-methoxy-3-(3-tetrahydrofuryloxy)phenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoate

gg) Ethyl *N*-[4-methoxy-3-((3R)-tetrahydrofuryloxy)phenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoate

hh) Ethyl *N*-[3-(2-methoxyethoxy)-4-methoxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoate

ii) Ethyl *N*-[4-methoxy-3-(2-(2-pyridyl)ethyl)oxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoate

jj) tert-Butyl N-(3-Cyclobutyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

kk) tert-Butyl N-(3-Cyclohexyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

ll) tert-Butyl N-(3-Cycloheptyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

mm) tert-Butyl N-(4-Methoxy-3-(4-pyranyloxy)phenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

nn) tert-Butyl N-(3-[2.2.2-Bicyclooctanyl]oxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

oo) tert-Butyl N-(3-Cyclobutyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

pp) tert-Butyl N-(3-Cyclohexyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

qq) tert-Butyl N-(4-Methoxy-3-(2-(2-Pyridylethoxy))phenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

rr) tert-Butyl N-(3,4-Dimethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

ss) tert-Butyl N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

tt) tert-Butyl N-(3-Isopropoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

uu) tert-Butyl N-(3,4-Dimethoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

vv) tert-Butyl N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

ww) tert-Butyl N-[4-Methoxy-3-(1-propyl)oxyphenyl]-N-(3-pyridylmethyl)-3-aminobenzoate

xx) tert-Butyl N-[4-Methoxy-3-(2-propyl)oxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

yy) tert-Butyl N-(3-Cyclopropylethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

zz) tert-Butyl N-(3-Cyclobutylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate.

EXAMPLE 27 (Method C)

The following compounds were prepared in a similar manner as described in Example 17A by coupling a phenol with a boronic acid rather than coupling an aniline with a boronic acid:

a) 4-Methoxy-3-(4-methoxyphenoxy)-*N*-(3-pyridylmethyl)diphenylamine

b) 4-Methoxy-3-phenoxy-*N*-(3-pyridylmethyl)diphenylamine

c) 4-Methoxy-3-(4-methylphenoxy)-*N*-(3-pyridylmethyl)diphenylamine

d) 3-(4-Chlorophenoxy)-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

e) 3-[2-(4-Chlorophenyl)ethenyloxy]-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 28

The following compounds were prepared in a similar manner as described in Example 26:

a) 3-Cyclopentyloxy-3'-hydroxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

b) 3-Cyclopentyloxy-4'-hydroxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

c) 3-Cyclopropylmethoxy-4'-hydroxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 29 (Method A)

The following compounds were prepared in a similar manner as described in Example 1A:

a) 3'-(2-Bromoethoxy)-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 29 (Method B)

The following compounds were prepared in a similar manner as described in Example 1B:

a) 3-Cyclopentyloxy-4'-(2-methoxyethoxy)-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

b) 3-Cyclopentyloxy-4'-(3-methyl-1-butoxy)-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

c) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-4'-[(3*S*)-tetrahydrofuranyloxy]-diphenylamine

d) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-4'-[(3*R*)-tetrahydrofuranyloxy]-diphenylamine

e) 3-Cyclopentyloxy-4'-cyclopropylmethoxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

f) 4'-Cyclohexylethoxy-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

g) 4'-Cyclopentylethoxy-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

h) 3-Cyclopentyloxy-4-methoxy-4'-(1-methylpiperidin-4-yloxy)-*N*-(3-pyridylmethyl)diphenylamine

i) 3-Cyclopentyloxy-4-methoxy-4'-(1-methylpyrrolidin-3-yloxy)-*N*-(3-pyridylmethyl)diphenylamine

j) 3-Cyclopentyloxy-4-methoxy-4'-[2-(1-methylpyrrolidin-2-yl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

k) 3-Cyclopentyloxy-4-methoxy-4'-[2-(1-pyrrolidinylethoxy)-*N*-(3-pyridylmethyl)diphenylamine

l) 3-Cyclopentyloxy-4-methoxy-4'-[2-(6-methylpyridyl)methoxy)-*N*-(3-pyridylmethyl)diphenylamine

m) 3-Cyclopentyloxy-4-methoxy-4'-[3-(1-methylpiperidinyl)methoxy]-*N*-(3-pyridylmethyl)diphenylamine

n) 3-Cyclopentyloxy-4-methoxy-4'-[2-(1-methylpiperidinyl)methoxy]-*N*-(3-pyridylmethyl)diphenylamine

o) 3-Cyclopentyloxy-4-methoxy-4'-[2-(5-oxopyrrolidinyl)methoxy]-*N*-(3-pyridylmethyl)diphenylamine

p) 4'-[1-(3-Bromopropyl)oxy]-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

q) 3-Cyclopentyloxy-4-methoxy-4'-[2-(*N*-phthalimido)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 30

3-Cyclopentyloxy-4-methoxy-3'-[2-(1-piperidinyl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

To a solution of 3'-(2-bromoethoxy)-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine (17 mg, 0.03 mmol) in acetonitrile (1 mL) was added potassium carbonate (25 mg, 0.18 mmol) and piperidine (5 μL, 0.05 mmol) and the mixture was stirred at

60°C for 4 h. The mixture was partitioned between water (50 mL) and EtOAc (50 mL). The layers were separated and the organic layer was washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was loaded on an ISCO RediSep column (4.2g, silica) and the column was eluted with a linear gradient from 5% MeOH in EtOAc to 15% MeOH in EtOAc to give 11 mg of product. ^1H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.48 (d, 1H, J = 4.7), 7.64 (d, 1H, 8.2 Hz), 7.26-7.20 (m, 1H), 7.06 (t, 1H, J = 8.6 Hz), 6.81 (d, 1H, J = 9.2 Hz), 6.75-6.68 (m, 2H), 6.45-6.35 (m, 3H), 4.91 (s, 2H), 4.64 (p, 1H, J = 4.1 Hz), 4.00 (t, 2H, J = 6.2 Hz), 3.84 (s, 3H), 2.71 (t, 2H, J = 6.2 Hz), 2.47 (m, 4H), 1.90-1.70 (m, 6H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-3'-[2-(1-imidazolyl)ethoxy]-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

b) 3-Cyclopentyloxy-4-methoxy-3'-[2-(1-methylpiperazin-4-yl)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

c) 3-Cyclopentyloxy-4-methoxy-4'-[3-(2-methylpiperazin-4-yl)propoxy]-*N*-(3-pyridylmethyl)diphenylamine

d) 3-Cyclopentyloxy-4-methoxy-4'-[3-(1-methylpiperazin-4-yl)propoxy]-*N*-(3-pyridylmethyl)diphenylamine

e) 3-Cyclopentyloxy-4-methoxy-4'-[3-(2-morpholin-4-ylethylamino)propoxy]-*N*-(3-pyridylmethyl)diphenylamine

f) 4-Methoxy-3-(2-phenoxyethoxy)-*N*-(3-pyridylmethyl)diphenylamine

g) 3-[2-(4-Chlorophenoxy)ethoxy)-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

h) 4-Methoxy-3-(2-pyrrolidin-1-yl)ethoxy-*N*-(3-pyridylmethyl)diphenylamine

i) 4-Methoxy-3-(2-(4-methylpiperazin-1-yl)ethoxy)-*N*-(3-pyridylmethyl)diphenylamine

j) 3-[2-(4-Chlorophenylamino)ethoxy]-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 31

4'-Aminoethoxy-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

To a solution of *N*-(3-pyridylmethyl)-3'-[2-(2-phthalimido)ethoxy]-3-cyclopentyloxy-4-methoxydiphenylamine (0.39 g, 0.69 mmol) in MeOH (5 mL) was added hydrazine hydrate (1.0 mL, 20 mmol). After 6 h at room temperature, EtOAc was added (50 mL) and the precipitate was filtered off. The filtrate was washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was loaded on an ISCO RediSep column (10 g, silica). The column was washed with 10% MeOH in EtOAc (200 mL) and the product was eluted with 50% MeOH in EtOAc to yield 0.21 g. ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.42 (d, 1H, J = 3.8 Hz), 7.62 (d, 1H, 7.7 Hz), 7.20-7.10 (m, 1H), 6.91 (d, 2H, J = 9.0 Hz), 6.78 (d, 2H, J = 9.0 Hz), 6.70 (d, 1H, J = 8.6 Hz), 6.50-6.35 (m, 2H), 4.82 (s, 2H), 4.54 (p, 1H, J = 4.1 Hz), 3.90 (t, 2H, J = 6.1 Hz), 3.74 (s, 3H), 3.01 (m, 2H), 1.86-1.70 (m, 8H), 1.65-1.45 (m, 2H).

EXAMPLE 32

The following compounds were prepared in a similar manner as described in Example 21:

a) 3-Cyclopentyloxy-4'-(2-methanesulfonylamino)ethoxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

b) 3-Cyclopentyloxy-4'-(2-ethanesulfonylamino)ethoxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

c) 3-Cyclopentyloxy-4-methoxy-4'-[2-(2-propanesulfonylamino)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

d) 3-Cyclopentyloxy-4-methoxy-4'-[2-(1-propanesulfonylamino)ethoxy]-*N*-(3-pyridylmethyl)diphenylamine

e) 4'-[2-(1-Butanesulfonylamino)ethoxy]-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

EXAMPLE 33

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)aniline

To a mixture of 100 mg N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-bromoaniline (0.22 mmol) and 57 mg of morpholine (0.66 mmol) in 5 mL of toluene was added 66 mg of sodium *t*-butoxide (0.66 mmol) and a mixture of 12 mg of tri-*t*-butylphosphonium tetrafluoroborate and 18 mg of tris(dibenzylidineacetone)dipalladium(0). The mixture was stirred for 16 h and filtered through celite. The celite was washed with 3 X 5 mL of toluene and the filtrate was concentrated in vacuo. The residue was purified by column chromatography eluting with 85%-90% EtOAc in hexanes to give 21 mg of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)anilin. [MW 461.559; ESMS *m/z* 462 $(M+H)^+$]

The following compounds were prepared in a similar manner as described above:

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-N-methyl-1-piperazinyl)aniline [MW 474.602; ESMS *m/z* 475 $(M+H)^+$]

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1-piperazinyl)aniline [MW 460.575; ESMS *m/z* 461.1 $(M+H)^+$]

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N,N-diethylamino)aniline [MW 447.576; ESMS *m/z* 448 $(M+H)^+$]

EXAMPLE 33A

N-methylpiperazine N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1-piperazinyl)aniline

To a mixture of 100 mg of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-bromoaniline (0.22 mmol) and 90 mg of 1-t-butoxycarbonylpiperazine (0.50 mmol) in 5 mL of toluene was added 50 mg of sodium t-butoxide (0.5 mmol), 15 mg of tri-t-butylphosphonium tetrafluoroborate (0.05 mmol) and 25 mg of tris(dibenzylidineacetone)dipalladium(0) (0.028 mmol). The mixture was stirred for 16 h and filtered through celite. The celite was washed with 3 X 5 mL of toluene and the filtrate was concentrated in vacuo. The residue was purified by column chromatography eluting with 75% EtOAc in hexanes. The purified residue was taken up in 20% TFA in dichloromethane and allowed to stand overnight and the solvent was removed in vacuo. The residue was partitioned between EtOAc and water and the aqueous layer was adjusted to pH = 7 with saturated sodium bicarbonate solution. The EtOAc layer was separated, washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography eluting with 5%-15% MeOH in EtOAc to give 10 mg of product as a brown foam.

EXAMPLE 34

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methanesulfonylaniline

To a mixture of 350 mg of mCPBA and 60 μL of TFA in 10 mL of dichloromethane at 0°C, was added a solution of 300 mg of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminothioanisole in 5 mL of dichloromethane. The mixture was allowed to warm to room temperature over 30 min and partitioned between dichloromethane and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography eluting with 85%-95% EtOAc in hexanes to yield 25 mg of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methanesulfonylaniline as a brown solid. [MW 454.544; ESMS *m/z* 455 $(M+H)^+$]

The following compounds were prepared in a similar manner as described above:
N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-methylsulfonylaniline as a brown solid. [MW 454.544; ESMS m/z 455 (M+H)+]

EXAMPLE 35

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline

To a solution of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoic acid (140 mg, 0.33 mmol), methanesulfonamide (38 mg, 0.40 mmol), and DMAP (49 mg, 0.40 mmol) in dichloromethane (2 mL) at room temperature was added EDCI (77 mg, 0.40 mmol) in one portion and the mixture was stirred at room temperature

for 16h. The mixture was partitioned between water (25 mL) and EtOAc (25 mL) and the pH was adjusted to 5-6 with 1.0N HCl. The EtOAc was separated, washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a linear gradient from 0% to 10% MeOH in EtOAc to give N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline (84 mg, 50% yield).). ^{1}H NMR (300 MHz) δ 8.54 (br,1H), 8.46 (br,1H), 7.70 (d,J=8.9 Hz, 2H), 7.60 (d,J=7.8 Hz, 1H), 7.3-7.2 (m,1H), 6.9-6.8 (m,2H), 6.7-6.6 (m,3H), 4.94 (s,2H), 4.84 (m,1H), 4.0-3.8 (m,7H), 3.34 (s,3H), 2.08 (m,2H).

Analogously prepared are:

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-methylsulfonylaminocarbonylaniline	MW 495.597	ESMS m/z 496.2 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-(2-methylphenyl)sulfonylaminocarbonylaniline	MW 571.695	ESMS m/z 572.2 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-phenylsulfonylaminocarbonylaniline	MW 557.668	ESMS m/z 558.3 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-phenylsulfonylaminocarbonylaniline	MW 557.668	ESMS m/z 558.3 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline	MW 495.597	ESMS m/z 496.3 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 577.63	ESMS m/z 578 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridylmethyl)-4-phenylsulfonylaminocarbonylaniline	MW 628.53	ESMS m/z 628, 629 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridylmethyl)-4-methylsulfonylaminocarbonylaniline	MW 566.459	ESMS m/z 567.9 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-ethylsulfonylaminocarbonylaniline	MW 511.596	ESMS m/z 512.2 (M+H)+

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2-fluorophenyl)sulfonylaminocarbonylaniline	MW 577.63	ESMS m/z 578.2 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-methoxyphenyl)sulfonylaminocarbonylaniline	MW 589.666	
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline	MW 594.085	ESMS m/z 594.2 596.2 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline	MW 533.549	
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-phenylsulfonylaminocarbonylaniline	MW 595.62	
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-phenylsulfonylaminocarbonylaniline	MW 559.64	ESMS m/z 559.9 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-3-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 593.648	ESMS m/z 594.1 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-methylsulfonylaminocarbonylaniline	MW 533.549	
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-phenylsulfonylaminocarbonylaniline	MW 595.62	
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline	MW 630.065	ESMS m/z 629.9 632.0 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2-fluorophenyl)sulfonylaminocarbonylaniline	MW 613.61	ESMS m/z 614 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,4-difluorophenyl)sulfonylaminocarbonylaniline	MW 631.601	ESMS m/z 632.1 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3,4-difluorophenyl)sulfonylaminocarbonylaniline	MW 631.601	ESMS m/z 632.1 (M+H)+

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1,1-dimethylethyl)sulfonylaminocarbonylaniline	MW 575.63	ESMS m/z 576.1 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(5-chloro-2-thienyl)sulfonylaminocarbonylaniline	MW 636.094	ESMS m/z 636.0 638.0 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-thienyl)sulfonylaminocarbonylaniline	MW 601.648	ESMS m/z 602 (M+H)+
N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 593.527	ESMS m/z 594.1 (M+H)+
N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline	MW 593.527	ESMS m/z 594.1 (M+H)+
N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline	MW 609.982	ESMS m/z 610.2 612.0 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-cyanophenyl)sulfonylaminocarbonylaniline	MW 620.63	ESMS m/z 621.1 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 613.61	ESMS m/z 614.1 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2-thienyl)sulfonylaminocarbonylaniline	MW 601.648	ESMS m/z 602 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline	MW 613.61	ESMS m/z 614 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-cyanophenyl)sulfonylaminocarbonylaniline	MW 584.65	ESMS m/z 585.1 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(2,6-difluorobenzyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 612.622	
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline	MW 577.63	ESMS m/z 578.2 (M+H)+

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,4-difluorophenyl)sulfonylaminocarbonylaniline	MW 595.62	ESMS m/z 596.1 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3,4-difluorophenyl)sulfonylaminocarbonylaniline	MW 595.62	ESMS m/z 596.1 (M+H)+
N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline	MW 578.086	ESMS m/z 578.1 580.1 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-fluorobenzyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 594.632	ESMS m/z 595.1 (M+H)+
N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 561.631	ESMS m/z 562.1 (M+H)+
N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline	MW 561.631	ESMS m/z 562.1 (M+H)+
N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-ethylsulfonylaminocarbonylaniline	MW 547.576	ESMS m/z 548.1 (M+H)+
N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(3-cyanophenyl)sulfonylaminocarbonylaniline	MW 618.658	ESMS m/z 619.1 (M+H)+
N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 611.638	ESMS m/z 612.2 (M+H)+
N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(3-fluorophenyl)sulfonylaminocarbonylaniline	MW 611.638	ESMS m/z 612.1 (M+H)+
N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline	MW 628.093	ESMS m/z 628.2 630.1 (M+H)+
N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(2,4-difluorophenyl)sulfonylaminocarbonylaniline	MW 553.583	ESMS m/z 554.1 (M+H)+
N-(3,4-Bisdifluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylsulfonylaminocarbonylaniline	MW 513.466	ESMS m/z 514 (M+H)+
N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-ethylsulfonylaminocarbonylaniline	MW 495.597	
N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)sulfonylaminocarbonylaniline	MW 535.593	

N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3-chlorophenyl)sulfonylaminocarbonylaniline	MW 552.048	ESMS m/z 552.0 554.1 (M+H)+
N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(3,4-difluorophenyl)sulfonylaminocarbonylaniline	MW 553.583	ESMS m/z 554.1 (M+H)+
N-(3-Ethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(2-thienyl)sulfonylaminocarbonylaniline	MW 523.631	ESMS m/z 524.1 (M+H)+

EXAMPLE 36

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(aminosulfonyl)aniline

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,5-dimethylpyrrol-1-yl)sulfonylaniline (0.533g, 1.0 mmol) was taken up in TFA (90 mL) and water (30 mL). The mixture was refluxed for 2h and concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The EtOAc layer was separated, washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a linear gradient of 0-10% MeOH in EtOAc to yield N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(aminosulfonyl)aniline (0.29 g, 64% yield). ^{1}H NMR (300 MHz) δ 8.56 (br,1H), 8.52 (br,1H), 7.66 (d,*J*=9.0 Hz, 2H), 7.70-7.55 (m,1H), 7.30-7.25(m,1H), 6.95-6.80 (m,2H), 6.7-6.6 (m,3H), 4.95 (s,2H), 4.93 (s,2H), 4.85 (m,1H), 4.0-3.8 (m,7H), 2.11 (m,2H).

EXAMPLE 37

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylcarbonylaminosulfonylaniline

To a solution of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(aminosulfonyl)aniline (45 mg, 0.1 mmol), acetic acid (12 mg, 0.2 mmol), and DMAP (26 mg, 0.2 mmol) in dichloromethane (2 mL) at room temperature was added EDCI (40 mg, 0.2 mmol) in one portion and the mixture was stirred at room temperature for 16h. The mixture was partitioned between water (25 mL) and EtOAc (25 mL) and the pH was adjusted to 5-6 with 1.0N HCl. The EtOAc was separated, washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a linear gradient from 0% to 10% MeOH in EtOAc to give N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylcarbonylaminosulfonylaniline (19 mg, 39% yield).). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (br,1H), 8.47 (br,1H), 7.72 (d,J=7.5 Hz,1H), 7.60 (d,J=9.0 Hz,2H), 7.4-7.3 (m,1H), 7.01 (d,J=9.3 Hz,1H), 6.9-6.8 (m,2H), 6.73 (d,J=9.0 Hz,2H), 4.95 (s,2H), 4.80 (m,1H), 3.9-3.7 (m,7H), 2.08 (m,2H), 1.86 (s,3H).

Analogously prepared are:

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-cyclopentylmethylcarbonylaminosulfonylaniline	MW 565.688	ESMS m/z 566.1 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-fluorophenyl)carbonylaminosulfonylaniline	MW 577.63	ESMS m/z 578 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(1-ethyl-5-methylpyrazol-4-yl)carbonylaminosulfonylaniline	MW 591.686	ESMS m/z 592 (M+H)+

EXAMPLE 38

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-hydroxymethylaniline

Into a flask containing 38 mg (0.090 mmol) of N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid was added 2 mL of dry THF. This mixture was placed under argon and 50 μL of BH_3-SMe_2 was added. This mixture was stirred at room temperature for 1.5 hours. Then, 0.1 mL of water was added and most of the solvent was removed followed by the addition of 5 mL of ethyl acetate. The resulting white solid was filtered and the solvent was removed to give N-(4-methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-hydroxymethylaniline (23 mg, 0.057 mmol) as a clear oil.

Analogously prepared are:

N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-hydroxymethylaniline (MW 442.46; ESMS, m/z 443.1 (M+H)+),

N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-hydroxymethylaniline (MW 406.479; ESMS, m/z 407.2 (M+H)+).

Example 39

3-Cyclopentyloxy-4-methoxy-N-(3-aminocarbonylphenyl)-N-(3-pyridylmethyl)aniline

To a solution of 3-cyclopentyloxy-4-methoxy-N-(3-carboxyphenyl)-N-(3-pyridylmethyl)aniline (50 mg, 0.125 mmol) in 1 mL of DMF at room temperature was added 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (50 mg, 0.20 mmol). The mixture was warmed slightly until everything was in solution, then cooled to room temperature and stirred for 1h. 5 drops of ammonium hydroxide (28-30%) was added and the mixture was stirred for an additional hour. The mixture was partitioned between water (25 mL) and EtOAc (25 mL). The EtOAc fraction was separated, washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in*

vacuo. The residue was purified by column chromatography eluting with a linear gradient from 0% to 10% MeOH in EtOAc to give 3-cylclopentyloxy-4-methoxy-N-(3-aminocarbonylphenyl)-N-(3-pyridylmethyl)aniline (28 mg, 54% yield) as a white solid. EIMS (*m/z*) = 418 $(M+H)^+$

Analogously prepared are:

3-Cyclopentyloxy-4-methoxy-N-(3-methylaminocarbonylphenyl)-N-(3-pyridylmethyl)aniline (MW 431.533),

3-Cyclopentyloxy-4-methoxy-N-(3-(2-hydroxyethyl)aminocarbonylphenyl)-N-(3-pyridylmethyl)aniline (MW 461.559).

Example 40

3,4-Bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(3-(4-methoxypyridylmethyl))aniline

To a solution of 3,4-bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(3-(4-chloropyridylmethyl))aniline (20 mg, 0.042 mmol) in N-methylpyrrolidinone (1 mL) was added methanol (1 mL) and sodium methoxide (25 mg, 0.46 mmol). The mixture was heated at 120 °C in a sealed tube for 16h. The mixture was partitioned between water (25 mL) and EtOAc (25 mL). The EtOAc fraction was separated, washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a linear gradient from 0% to 10% MeOH in EtOAc to give 3,4-bisdifluoromethoxy-N-(3-carboxyphenyl)-N-(3-(4-methoxypyridylmethyl))aniline (5 mg, 26% yield) as a brown solid. EIMS (*m/z*) = 467 $(M+H)^+$

Analgously prepared is:

3,4-Bis(difluoromethoxy)-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-(4-methoxypyridylmethyl))aniline.

Example 41

3-Cyclopentyloxy-4-methoxy-N-phenyl-N-(3-(2-ethoxypyridylmethyl))aniline

3-Cyclopentyloxy-4-methoxy-N-phenyl-N-(3-(2-chloropyridylmethyl))aniline (30 mg, 0.074 mmol) was dissolved in 2M ethanolic KOH (2 mL) and heated at 120 °C in a sealed tube for 16h. The mixture was partitioned between water (25 mL) and EtOAc (25 mL). The EtOAc was separated, washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 15% EtOAc in hexanes to give 3-cyclopentyloxy-4-methoxy-N-phenyl-N-(3-(2-ethoxypyridylmethyl))aniline (32 mg, 100% yield) as a pale yellow solid. EIMS (*m/z*) = 419 $(M+H)^+$; (MW 418.534).

Example 42

3-Cyclopentyloxy-4-methoxy-N-(4-amino-3-carboxyphenyl)-N-(3-pyridylmethyl)aniline

A solution of 3-cyclopentyloxy-4-methoxy-N-(3-carboxy-4-nitrophenyl)-N-(3-pyridylmethyl)aniline (200 mg, 0.43 mmol) in 20 mL of EtOAc and 5 mL of EtOH was hydrogenated at atmospheric pressure over 20 mg of PtO_2 with stirring for 16 hours. The catalyst was removed by filtration and the solution concentrated. The residue was chromatographed over SiO_2 using MeOH/DCM (1/10) as eluant. The oily residue was further purified by trituration with 1 mL of CH_3CN to give 52 mg (28% yield) of the target compound.

Example 43

3-Cyclopentyloxy-4-methoxy-N-(4-acetamido-3-carboxyphenyl)-N-(3-pyridylmethyl)aniline

A solution of 3-cyclopentyloxy-4-methoxy-N-(3-carboxy-4-nitrophenyl)-N-(3-pyridylmethyl)aniline (200 mg, 0.43 mmol) in 35 mL of EtOAc and 0.1 mL (1.08 mmol) of acetic anhydride was hydrogenated at atmospheric pressure over 20 mg of PtO_2 with stirring for 16 hours. The catalyst was removed by filtration and the solution concentrated. The residue was partitioned between 50 mL of DCM and 100 mL of brine. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was chromatographed over SiO_2 using MeOH/DCM (1/20) as eluant to give 105 mg (51% yield) of the target compound.

EXAMPLE 44

In Vitro Measurement of Type 4 Phosphodiesterase Inhibition Activity

Human PDE4 was obtained from baculovirus-infected Sf9 cells that expressed the recombinant enzyme. The cDNA encoding hPDE-4D6 was subcloned into a baculovirus vector.

Insect cells (Sf9) were infected with the baculovirus and cells were cultured until protein was expressed. The baculovirus-infected cells were lysed and the lysate was used as source of hPDE-4D6 enzyme. The enzyme was partially purified using a DEAE ion exchange chromatography. This procedure can be repeated using cDNA encoding other PDE-4 enzymes.

Assay:

Type 4 phosphodiesterases convert cyclic adenosine monophosphate (cAMP) to 5'-adenosine monophosphate (5'-AMP). Nucleotidase converts 5'-AMP to adenosine. Therefore the combined activity of PDE4 and nucleotidase converts cAMP to adenosine. Adenosine is readily separated from cAMP by neutral alumina columns. Phosphodiesterase inhibitors block the conversion of cAMP to adenosine in this assay; consequently, PDE4 inhibitors cause a decrease in adenosine.

Cell lysates (40 ul) expressing hPDE-4D6 were combined with 50 ul of assay mix and 10 μl of inhibitors and incubated for 12 min at room temperature. Final concentrations of assay components were: 0. 4 ug enzyme, 10mM Tris-HCl (pH 7.5), 10mM $MgCl_2$, 3 uM cAMP, 0.002 U 5'-nucleotidase, and 3 x 10^4 cpm of [3H]cAMP. The reaction was stopped by adding 100 μl of boiling 5mN HCl. An aliquot of 75 μl of reaction mixture was transferred from each well to alumina columns (Multiplate; Millipore). Labeled adenosine was eluted into an OptiPlate by spinning at 2000 rpm for 2 min; 150 μl per well of scintillation fluid was added to the OptiPlate. The plate was sealed, shaken for about 30 min, and cpm of [^{3}H]adenosine was determined using a Wallac Triflux®.

All test compounds are dissolved in 100% DMSO and diluted into the assay such that the final concentration of DMSO is 0.1%. DMSO does not affect enzyme activity at this concentration.

A decrease in adenosine concentration is indicative of inhibition of PDE activity. pIC_{50} values were determined by screening 6 to 12 concentrations of compound ranging from 0.1 nM to 10,000 nM and then plotting drug concentration versus ^{3}H-adenosine concentration. Nonlinear regression software (Assay Explorer®) was used to estimate pIC_{50} values.

EXAMPLE 45 (Method A)

Passive Avoidance in Rats, an in vivo Test for Learning and Memory

The test was performed as previously described (Zhang, H.-T., Crissman, A.M., Dorairaj, N.R., Chandler, L.J., and O'Donnell, J.M., *Neuropsychopharmacology*, 2000, *23*, 198-204.). The apparatus (Model E10-16SC, Coulbourn Instruments, Allentown, PA) consisted of a two-compartment chamber with an illuminated compartment connected to a darkened compartment by a guillotine door. The floor of the darkened compartment consisted of stainless steel rods through which an electric foot-shock could be delivered from a constant current source. All experimental groups were first habituated to the apparatus the day before the start of the experiment. During the training, the rat (Male Spraque-Dawley (Harlan) weighing 250 to 350 g) was placed in the illuminated compartment facing away from the closed guillotine door for 1 minute before the door was raised. The latency for entering the darkened compartment was recorded. After the rat entered the darkened compartment, the door was closed and a 0.5 mA electric shock was administered for 3 seconds. Twenty-four hours later, the rat was administered 0.1 mg/kg MK-801 or saline, 30 minutes prior to the injection of saline or test compound (dosed from 0.1 to 2.5 mg/kg, i.p.), which was 30 minutes before the retention test started. The rat was again placed in the illuminated compartment with the guillotine door open. The latency for entering the darkened compartment was recorded for up to 180 seconds, at which time the trial was terminated.

All data were analyzed by analyses of variance (ANOVA); individual comparisons were made using Kewman-Keuls tests. Naïve rats required less than 30 seconds, on average, to cross from the illuminated compartment to the darkened compartment. However, 24 hours after the electric shock exposure, most rats pretreated with vehicle did not re-enter the darkened compartment; the average latency was increased up to 175 seconds ($p < 0.001$). Pretreatment with MK-801 (0.1 mg/kg) markedly reduced this latency when compared to the vehicle ($p<0.001$). This amnesic effect of MK-801 is reversed in a statistically significant manner by actual test compounds in a dose-dependent fashion (e.g., 3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl) diphenylamine, Effective dose range = 0.5 to 2.5 mg/kg, i.p.; and *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid, effective dose range = 0.1 to 2.5 mg/kg, ip).

EXAMPLE 45 (Method B)

Radial arm maze task in Rats, an in vivo Test for Learning and Memory

The test was performed as previously described (Zhang, H.-T., Crissman, A.M., Dorairaj, N.R., Chandler, L.J., and O'Donnell, J.M., *Neuropsychopharmacology*, 2000, *23*, 198-204.). Five days after initial housing, rats (male Spraque-Dawley (Harlan) weighing 250 to 350 g) were placed in the eight-arm radial maze (each arm was 60x10x12 cm high; the maze was elevated 70 cm above the floor) for acclimation for two days. Rats were then placed individually in the center of the maze for 5 minutes with food pellets placed close to the food wells, and then, the next day, in the wells at the end of the arms; 2 sessions a day were conducted. Next, four randomly selected arms were then baited with one pellet of food each. The rat was restricted to the center platform (26 cm in diameter) for 15 seconds and then allowed to move freely throughout the maze until it collected all pellets of food or 10 minutes passed, whichever came

first. Four parameters were recorded: 1) working memory errors, i.e., entries into baited arms that had already been visited during the same trial; 2) reference memory errors, i.e., entries into unbaited arms; 3) total arm entries; and 4) the test duration (seconds), i.e., the time spent in the collection of all the pellets in the maze. If the working memory error was zero and the average reference memory error was less than one in five successive trials, the rats began the drug tests. MK-801 or saline was injected 15 minutes prior to vehicle or test agent, which was given 45 minutes before the test. Experiments were performed in a lighted room, which contained several extra-maze visual cues.

All data were analyzed by analyses of variance (ANOVA); individual comparisons were made using Kewman-Keuls tests. Compared to control, MK-801 (0.1 mg/kg, i.p.) increased the frequencies of both working and reference memory errors ($p<0.01$). This amnesic effect of MK-801 on working memory is reversed in a statistically significant manner by the administration of actual test compounds in a dose-dependent fashion (e.g., 3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine, Effective dose = 2.5 mg/kg, i.p.; $p<0.01$)

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

While the invention has been illustrated with respect to the production and of particular compounds, it is apparent that variations and modifications of the invention can be made without departing from the spirit or scope of the invention.